three biostatisticians, two biochemists, two epidemiologists, one biophysicist, one pathologist, one pharmacologist, and one endocrinologist. The former Director, now a consultant, is the only physician associated with the office.

Agenda and Procedures

CAG does not initiate its own assessments; instead, it responds to requests from regulatory (program) offices in EPA. It does, however, set its own priorities in consultation with the program offices, on the basis of the workload of requests and the urgency of the need for the assessments. Although it serves as a risk assessment body for the whole Agency, not all programs in EPA use CAG. The most notable exception is the Office of Toxic Substances. Apparently, one factor cited by program offices as leading to this lack of use is the length of time CAG requires to complete an assessment.

Since 1976, CAG has prepared assessments for approximately 150 chemicals. The length and scope of the documents produced vary with the data available, with their purpose, and with the needs of the requesting office. They can range from brief and preliminary literature reviews relevant to hazard identification or tentative estimates of risk as a function of dose to complete and thorough literature reviews leading to a comprehensive risk characterization. In-depth evaluations may or may not include quantitative dose-response assessments. As an example of its work agenda, CAG has covered 41 chemicals for the Agency's Office of Air Quality Planning and Standards. In-depth evaluations were performed for nine (see Table III-4), and preliminary assessments for 32.

Methods and Use of Guidelines

The risk assessments performed by this group are based on Agency guidelines developed initially by CAG in 1976 for use by the entire Agency. These guidelines have been revised after initial publication, and some of the changes have also been published (EPA, 1979, 1980). Normally, individual assessment documents produced do not reexamine or indeed articulate underlying guidelines; rather, the reader is presumed to know that EPA and CAG rely on guidelines that embody particular choices among several

FIGURE III-3 Organization chart of EPA.

TABLE III-4 Substances Fully Evaluated by the Carcinogen Assessment Group for the EPA Office of Air Quality Planning and Standards

Arsenic	Methyl chloroform[a]
Benzene	Methylene chloride[a]
Vinyl chloride	Tetrachloroethylene[a]
Acrylonitrile[a]	Trichloroethylene[a]
Coke-oven emission[a]	

[a]Under review as of October 1982.

inference options available. Also, the changes made in the guidelines have not, in many cases, been formally acknowledged; i.e., the current guidelines do not exist in a single publicly accessible written document. CAG's use of guidelines, especially for hazard identification, has been regarded by some EPA review panels--notably, the Subcommittee on Airborne Carcinogens--as too inflexible, possibly misleading, and interfering with critical analysis of underlying data. In fact, the initial published guidelines (EPA, 1976) did permit different interpretations of data and the use of different risk assessment methods; however, the methods embodied in CAG assessments and those related to dose-response assessment and published in EPA's Water Quality Methodology for Carcinogens do not reflect this flexibility. The misunderstandings experienced with the Subcommittee on Airborne Carcinogens (and other review bodies) have stemmed to a great degree from the facts that CAG's guidelines are in flux, remain unwritten, and are not presented in the individual assessment documents provided to the review committees. As a result, reviewers are likely to be unaware of the operational ground rules used in interpreting carcinogenicity data and developing risk estimates. The absence of an explicit discussion of the application of Agency guidelines and of discussion of the rationale for the choices made in a risk assessment blurs the distinction between science and policy considerations in CAG assessments.

Peer Review

Drafts are reviewed by all members of the CAG staff and its Director. Drafts are also usually sent for review on an ad hoc basis to knowledgeable persons outside the agency. However, this review process is not part of the public record, and criticism may be accepted or rejected at CAG's discretion. The lack of adequate procedures to ensure that peer review comments are given proper consideration may lessen any benefits to be derived from peer review early in the process of developing a risk assessment. Draft risk assessments are usually reviewed by the Director of the Office of Health and Environmental Assessment, directors of other units in this office, and Office of Research and Development staff before being submitted to the requesting program office. CAG assessments are often submitted to committees of EPA's Science Advisory Board or to the Scientific Advisory Panel for peer review. Such reviews take place in public sessions, in accordance with the requirements of the Federal Advisory Committee Act. They provide an opportunity for interested members of the public to review CAG documents and to communicate criticisms to the reviewing committee and EPA. Reviews of CAG assessments by EPA panels have been mixed, with some panels, such as the Scientific Advisory Panel, often approving the assessments and others finding numerous shortcomings related to both substance and format (e.g., the Subcommittees on Arsenic as a Possible Hazardous Air Pollutant and on Airborne Carcinogens of the Agency's Science Advisory Board). This public review process usually leads to revisions.

NIOSH-OSHA

The Occupational Safety and Health Act of 1970 created two new organizations: OSHA and NIOSH. OSHA was a new component of the Department of Labor. NIOSH was placed in the Department of Health, Education, and Welfare, now the Department of Health and Human Services. Since 1973, NIOSH has been a part of the Centers for Disease Control in the U.S. Public Health Service. The common mission set for both agencies was the protection of the health of American workers. NIOSH's primary functions included the conduct of research and development of criteria for recommendations to OSHA for occupational health standards. In addition, the Act authorized NIOSH to "develop and estab-

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 2 of 48

lish recommended occupational safety and health standards." Although it is not technically correct to refer to NIOSH criteria documents simply as risk assessments, because the documents contain additional information concerning risk management (e.g., engineering considerations) as well as recommended standards, the documents normally included sections that dealt with the adverse health effects of the substances being considered. The health-effects sections would correspond to the Committee's definition of hazard identification.

The legislative history of the Act makes it clear that Congress intended a close coupling between NIOSH's recommendations and OSHA's standards. Nevertheless, relatively few NIOSH criteria documents have led to OSHA standards. This disjunction between the two agencies has stemmed from the difficulty of coordinating two organizations that are physically separated and responsible to different departments. As mentioned earlier, the degree to which OSHA has relied on NIOSH for its scientific expertise has varied. In the early 1970s, OSHA relied heavily on NIOSH for evaluation of health effects; later, OSHA developed its own staff of health scientists and, with considerable help from consultants and contractors, performed its own risk assessments to support agency standard-setting activities.

Because OSHA conducts its own assessments of risk, as well as setting standards, and NIOSH does risk assessments and recommends standards, the relation of NIOSH and OSHA as it has existed since 1976 represents, in some sense, duplication, rather than true extra-agency separation. The earlier relation between the two agencies is, however, an example of extra-agency separation. This section focuses on NIOSH's production of criteria documents during both phases and reflects procedures used throughout the 1970s.

Agenda and Procedures

In the past, NIOSH had an elaborate procedure for setting priorities, which included soliciting nominations of candidate substances from OSHA and the public. In practice, however, before 1976, NIOSH's criteria document agenda was set by agency personnel and the Director, on the basis of their views of the seriousness of various occupational hazards and the number of workers exposed to such hazards. OSHA played little or no role in the selection process,

and NIOSH's agenda for documents therefore did not reflect or greatly influence OSHA's regulatory agenda. One cause of this lack of correlation between the two schedules was their physical and organizational separation. In the late 1970s, NIOSH did receive communications from OSHA that led NIOSH to begin production of process- and industry-oriented criteria documents. Table III-5 lists criteria documents transmitted to OSHA.

Methods and Use of Guidelines

Preparation of a criteria document involved a preliminary review of literature and the identification of gaps in the relevant knowledge. This gap analysis was fed into NIOSH's research planning and led to research directed at filling the gaps. Brief studies could be completed in time for their results to be incorporated into the document. Others would continue after the document was completed and sometimes resulted in revision or updating. The literature review and preparation of a draft document were commonly performed by an external contractor under the supervision of NIOSH personnel. Because NIOSH does not have written guidelines for risk assessment, whether personnel preparing the documents used similar approaches to evaluate data and reach conclusions regarding risks is unclear. NIOSH's failure to develop risk assessment guidelines has helped to obscure the distinction between scientific and policy judgments in the risk assessment process. Although the rationale for separating NIOSH from OSHA has been to allow an independent scientific evaluation without the consideration of economic implications that is necessary in OSHA rule-making activities, the effectiveness of this institutional separation in eliminating the effects of such risk management considerations on the conduct of risk assessment by NIOSH is difficult to determine.

Peer Review

The initial review of a draft criteria document was typically performed by NIOSH staff in the same division of the agency that produced the document. The division draft was then submitted to other NIOSH divisions for review. This was followed by a review performed by knowledgeable experts from industry, labor organizations,

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 3 of 48

TABLE III-5 NIOSH Criteria Documents Sent to OSHA by May 1982

Substance or Subject	Transmitted to OSHA
Acetylene	1976
Acrylamide	1976
Acrylonitrile	1977
Alkanes	1977
Allyl chloride	1976
Ammonia	1974
Antimony	1978
Arsenic, inorganic	1974, 1975
Asbestos	1972, 1976
Asphalt fumes	1977
Benzene	1974, 1977
Benzoyl peroxide	1977
Benzyl chloride	1978
Beryllium	1972, 1977
Boron trifluoride	1976
Cadmium	1976
Carbaryl	1976
Carbon black	1978
Carbon dioxide	1976
Carbon disulfide	1977
Carbon monoxide	1972
Carbon tetrachloride	1975, 1976
Chlorine	1976
Chloroform	1974, 1976
Chlorophene	1977
Chromic acid	1973
Chromium (VI)	1975
Coal-gasification plants	1978
Coal-liquefaction (Vols. I and II)	1981
Coal-tar products	1977
Cobalt	1981
Coke-oven emission	1973
Confined spaces (as workplaces)	1980
Cotton dust	1974
Cresol	1978
Cyanide, hydrogen, and cyanide salts	1976
Decomposition products of fluorocarbon	1977
Dibromochloropropane	1977
Diisocyanates	1978
Dinitro-o-cresol	1978
Dioxane	1977
Emergency egress from elevated work stations	1975
Epichlorohydrin	1976
Ethylene dibromide	1977
Fibrous glass	1977
Fluorides, inorganic	1975
Formaldehyde	1976
Furfuryl alcohol	1979
Glycidyl ethers	1978
Hot environments	1972
Hydrazines	1978

TABLE III-5 (Continued)

Substance or Subject	Transmitted to OSHA
Hydrogen fluoride	1976
Hydrogen sulfide	1977
Hydroquinone	1978
Identification system for occupationally hazardous materials	1974
Isopropyl alcohol	1976
Kepones	1976
Ketones	1978
Lead, inorganic	1973, 1977
Logging--from felling to first haul	1976
Malathion	1976
Mercury, inorganic	1973
Methyl alcohol	1976
Methylene chloride	1976
Methyl parathion	1976
Nickel, inorganic and compounds	1977
Nitric acid	1976
Nitriles	1978
Nitrogen oxides	1976
Nitroglycerin--ethylene glycol dinitrate	1978
Noise	1972
Organotin compounds	1976
Parathion	1976
Pesticide manufacturing and formulation	1978
Phenol	1976
Phosgene	1976
Polychlorinated biphenyls	1977
Refined petroleum solvent	1977
Silica, crystalline	1974
Sodium hydroxide	1975
Sulfur dioxide	1974, 1977
Sulfuric acid	1974
1,1,2,2-Tetrachloroethane	1976
Tetrachloroethylene	1976
Thiols: n-alkane mono-, cyclohexane, and benzene	1978
Toluene	1973
Toluene diisocyanate	1973, 1978
o-Toluidine	1978
1,1,1-Trichloroethane	1976
Tungsten and cemented tungsten carbide	1977
Ultraviolet radiation	1972
Vanadium	1977
Vinyl acetate	1978
Vinyl chloride	1974
Vinyl halides	1978
Waste anesthetic gases and vapors	1977
Xylene	1975
Zinc oxide	1975

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 4 of 48

and universities. In addition, other appropriate government agencies, professional associations, and trade organizations were invited to review the document. After these various reviews were complete and changes were made as deemed appropriate by division staff, the document was forwarded to the Director of NIOSH.

Several shortcomings of NIOSH criteria documents were cited in a recent review of the program funded by the agency: the lack of field experience of criteria document managers, the lack of critical analysis of data, and the alleged disregard of reviewers' comments. The latter claim highlights the importance of procedures that ensure that reviewers' comments are adequately addressed. The lack of critical analysis of data has been attributed at least in part to the facts that the documents were often developed by outside contractors and that NIOSH had little control over the personnel assigned to the contract staff.

COMMITTEES OF THE NATIONAL RESEARCH COUNCIL

The National Research Council (NRC) is the operating unit for the National Academy of Sciences' advisory function. As part of this advisory function, NRC has been called on by a number of regulatory agencies to perform risk assessments. Regulatory agencies request assessments by NRC for several reasons, including statutory requirements that particular agencies or programs consult with NRC, inadequacy of agency staff to perform the assessments (as in the case of the FDA request for a review of pre-1962 prescription drugs), and such political objectives as a desire for outside scientific support of an anticipated agency action or a desire to defuse or postpone controversy. Agencies remain free to accept or reject the analyses and conclusions included in NRC reports. NRC risk assessment reports are usually not sufficient by themselves to dictate specific regulatory action, and a separate assessment is usually conducted by the agency, even if in only the most perfunctory fashion.

NRC has done risk assessments for several agencies with jurisdiction over carcinogenic chemicals. However, NRC is in no real sense a centralized risk assessment body and is a very imperfect model for recent proposals to create such a body. First, most of the evaluative work of the NRC is actually performed by individual committees created on an ad hoc basis for each study. Thus, NRC is not a single risk assessment body, but

rather an umbrella for the work of many diverse, if outwardly similar, committees. Second, each ad hoc committee generally reports to a single agency and does not perform assessments for several bodies at once. The committees of NRC have been included in our survey as examples of ad hoc risk assessment groups that are entirely separate from government regulators. Table III-6 is a partial list of NRC reports (published since 1977) that examined the carcinogenic risks associated with exposure to particular chemicals.

Agenda and Procedures

Committee members are appointed on the strength of their professional qualifications; they may come from universities, industry, government, or another sector of society, but they do not serve as representatives of any agency, group, or institution unless they are specifically so designated on appointment. Occasionally when, by virtue of special expertise or for other reasons, persons affiliated with interested parties are placed on committees, every effort is made to achieve a balance of interests. In any case, all committee members are asked to complete a statement, "On Potential Sources of Bias," which includes information on sources of personal income, sources of research support, and more subtle forms of personal bias, including values held that may influence a member's judgment. The membership of every committee that will formulate a position, take an action, or prepare a report is reviewed by NRC staff and must be approved by the Chairman of NRC. The work of the committees is facilitated by professional and support staff employed by NRC.

The conduct of a study varies with its nature and objective, the time permitted to complete it, its political sensitivity, and the personalities involved. In general, committees have considerable latitude in carrying out their responsibilities and may hold public meetings and schedule technical conferences to collect pertinent information. Committees typically meet three to six times a year. Meetings are concerned with planning, discussions of issues and drafts of reports, and, later, the development of final conclusions and recommendations. Although a committee has much freedom in planning and executing its study and reaching its conclusions, several restrictions include the obvious necessity to respond to the charge stipulated in the contract, time and budgetary

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 5 of 48

TABLE III-6 Some NRC Reports Dealing with Carcinogenic Chemicals (1977-1982)

Report	Parent Unit[a]	Year
An Assessment of Mercury in the Environment	CPSMR	1977
An Evaluation of the Carcinogenicity of Chlordane and Heptachlor	CLS	1977
Drinking Water and Health	CLS	1977
Arsenic	CLS	1977
Nitrates	CPSMR	1978
Saccharin--Technical Assessment of Risks and Benefits	CLS	1978
Polychlorinated Biphenyls	CPSMR	1979
Drinking Water and Health, Vol. III	CLS	1980
The Alkyl Benzenes	CLS	1980
Formaldehyde--An Assessment of Its Health Effects	CLS	1980
Regulating Pesticides	CPSMR	1980
Aromatic Amines: An Assessment of the Biological and Environmental Effects	CLS	1981
Formaldehyde and Other Aldehydes	CLS	1981
The Health Effects of Nitrate, Nitrite, and N-Nitroso Compounds	CLS	1981
Indoor Pollutants	CLS	1981
Selected Aliphatic Amines and Related Compounds: An Assessment of the Biological and Environmental Effects	CLS	1981
Alternatives to the Current Use of Nitrite in Foods	CLS	1982
An Assessment of the Health Risks of Seven Pesticides for Termite Control	CLS	1982
Diet, Nutrition, and Cancer	CLS	1982
Drinking Water and Health, Vol. IV	CLS	1982
Quality Criteria for Water Reuse	CLS	1982
Possible Long-Term Health Effects of Short-Term Exposure to Chemical Agents, Vol. 1--Anticholinesterases and Anticholinergics	CLS	1982

[a]CPSMR = Commission on Physical Sciences, Mathematics, and Resources; CLS = Commission on Life Sciences.

limitations, and the necessity for a central NRC-monitored review of the final report.

In addition to providing scientific analyses on which policy or regulatory decisions can be based, NRC reports sometimes make specific recommendations for changes in government policy.

Methods and Use of Guidelines

NRC risk assessments are not easily classified or characterized. Because different committees prepare risk-related reports and NRC does not have any guidelines on the conduct of risk assessments for the committees to follow, approaches and final products show pronounced variations. The absence of guidelines, coupled with the occasional practice of not including a clear explanation of how conclusions concerning risk were reached or of the assumptions used in the quantitation of risk, has led to a blurring of the distinction between scientific and policy judgments made in the assessment of risks. The lack of guidelines has also led to inconsistencies in approach and final decisions among committees. However, the absence of specific guidance for interpreting data and for choosing methods of dose-response assessment or risk characterization is probably to be expected, inasmuch as NRC committees consist of scientific experts whose independent judgments are being sought. Probably only guidelines that are extremely flexible could be adopted by NRC. A subject of much discussion over the last several years has been the value of including quantitative assessments (in our terms, dose-response assessments or, if exposure data are incorporated, risk characterizations) in reports. The trend in recent years has been to include some form of a quantitative risk estimate.

Peer Review

Every report from the NRC is reviewed by a group other than the authors. The process of reviewing is overseen by the Report Review Committee. The reports likely to receive reviews coordinated by that Committee are those judged to have significant policy implications and likely to be controversial; most reports that address risk-related questions would be in this category. (The Report Review Committee also coordinates the review of noncontro-

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 6 of 48

versial reports on an ad hoc basis to monitor the overall quality of NRC reports.) A report not receiving such a review is reviewed under the auspices of its parent commission, independent office, or board. Report Review Committee review entails submission of a draft report to a set of reviewers selected in a cooperative process by the the parent body and the Report Review Committee. These reviewers are invited to comment on technical adequacy and accuracy (the expertness of the authors), on clarity and appropriateness of presentation, on response to charge, on cogency of recommendations with respect to data presented, and on degree of objectivity and freedom from bias. The committee and staff respond to reviewers' criticisms and suggestions, and the responses are examined by a monitor, usually a member of the Report Review Committee, to determine their appropriateness. Thus, a person outside the unit that prepared the report decides whether adequate consideration has been given to reviewers' comments. In cases of persistent and severe disagreement between reviewers and authors, the matter may be referred to the NRC chairman for resolution.

Like the regulatory agencies, NRC has been the subject of controversy in recent years. Some NRC committees have been accused of bias related to their judgments on the risks associated with the substances they are studying. The absence of a member from a discipline that is important for a balanced assessment of risk can also weaken the credibility of an NRC report. For example, an internal NRC study (1981) stated that, in a small sample of risk-related studies completed before 1979, such disciplines as epidemiology were often not represented on the rosters of committees whose subjects appeared to warrant such knowledge.

FDA'S DRUG EVALUATION PANELS

Under the Federal Food, Drug, and Cosmetic Act, FDA regulates the marketing of all medicines for human use--prescription pharmaceuticals, over-the-counter drugs, and biologic products, which are also subject to the 1902 Biologics Act. In its efforts to ensure the safety and effectiveness of drugs in these three classes, FDA has relied heavily on advisory panels composed primarily of scientists from academic medicine. Two major programs illustrate the important role of such independent expert panels in agency assessments of human

drugs: the Drug Efficacy Study, a review of the effectiveness of pre-1962 prescription drugs undertaken by NRC in 1966; and the over-the-counter Drug Review, in which advisory panels established directly by FDA have evaluated the effectiveness and safety of ingredients of such drugs.

Both the NRC review and the FDA-directed review enabled FDA to undertake systematic studies of product performance that would have overwhelmed the agency's own resources and personnel. The two reviews differed in a number of respects that may shed some light on optimal structures and procedures for scientific panels.

NRC Review

The 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act required that all new drugs be proved effective, as well as safe, and obliged FDA, after a 2-year grace period, to require proof of efficacy of all pre-1962 drugs. In discharging this obligation for prescription drugs, the agency turned to NRC to establish some 30 panels of six to eight experts in pharmaceutical therapy; each panel was responsible for a class of drugs.

The panels evaluated the data supplied to them by FDA and manufacturers and rated the drugs as effective, probably effective, possibly effective, ineffective, ineffective as a fixed combination, or inferior to other better or safer therapies for the same indications. Their main function was thus to assess therapeutic efficacy, not risk to patient health (except indirectly); all the drugs reviewed had been judged to be safe before original FDA approval. Nevertheless, the panels included comments on the safety of individual drugs, particularly those whose effectiveness was in doubt. An informal NRC coordinating group attempted to review each panel's ratings before forwarding them to FDA, in the hope of ensuring some consistency. In practice, however, the panel's verdicts reached FDA largely unreviewed.

The clinical and other data on which the panels relied came from FDA files, the medical and scientific literature, and the manufacturers of the drugs. The panels neither performed nor ordered any new research, although their assessments often identified subjects on which further studies were needed. The panels met and worked privately; apart from being invited to submit supporting data, manufacturers had no opportunity to participate in the panels' deliberations, nor did representatives of consumers or FDA staff.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 7 of 48

To reconstruct precisely how the panels worked or to determine what criteria for evaluation each followed is difficult. The predetermined categories in which they were to rate drugs produced apparent homogeneity in their results, but did not sharply confine or direct their analyses. Evidently, wide variations occurred among the panels. The panels' assessments were reported to FDA largely as statements of conclusions; many of the reports were only one or two paragraphs long. Explanations for the ratings typically took the form of bare references to published studies or invocations of the informed judgment of the panelists. In short, the panels provided verdicts, rather than documented evaluations.

The weight to be given the panels' assessments was not squarely addressed when FDA contracted for NRC assistance. Apparently, it was understood that FDA remained free to accept or reject a panel's judgment, but it must have expected to accept most of the panels' assessments when it contracted with NRC. The agency's primary goal was to spare its own scientific staff the enormous burden of evaluating the effectiveness of thousands of pre-1962 drugs. In practice, FDA has accorded substantial weight to the assessments provided by the NRC panels, usually accepting the rating provided and initiating appropriate regulatory action. A rating of less than "effective" led to notification of a drug manufacturer that more data were needed to support a claim of effectiveness; later (often years later), if data were still considered inadequate, the agency took steps to remove the drug from the market. Some of the agency's efforts provoked protracted litigation and administrative hearings. However, pharmaceutical manufacturers have acceded to the panels' judgments in the majority of instances, occasionally by withdrawing products from the market, more frequently by eliminating claims for which supporting evidence was lacking, and sometimes by sponsoring new clinical research. One important determinant of the acceptance of panel assessments was the commercial importance of the product or claim at issue. When a panel rating and ultimate FDA judgment jeopardized the continued marketing of an important product, the manufacturer often insisted on its full legal rights in the course of combating FDA's efforts at implementation.

FDA-Directed Drug Panels

The NRC review of pre-1962 drugs did not address the marketing status of most over-the-counter drugs. In 1972, FDA launched a second comprehensive review, this time on both the effectiveness and the safety of all active ingredients in over-the-counter drugs. At the outset of this review, FDA chartered 17 advisory committees representing therapeutic groupings. These 17 panels met a total of 522 times over a 9-year period; they reviewed 722 active ingredients for over 1,400 indications and submitted over 75 reports on different therapeutic categories, e.g., internal analgesics, antimicrobials, and vaginal contraceptives.

The central function of these review panels was to report and explain their assessments of the safety and effectiveness of the ingredients used in over-the-counter drugs. These reports were to set forth not only the panels' judgments rating each ingredient (as generally recognized as safe and effective, as unsafe or ineffective, or as requiring additional study), but also supporting documentation and rationale. The panel reports became treatises on the various therapeutic categories, some well over 1,000 pages long. The recommendation segments of the reports were considerably shorter.

FDA intended from the outset to rely heavily on the panels' assessments and thus insisted that they produce thoroughly documented findings. In addition, the panels were required to meet in public and to adhere to other requirements of the Federal Advisory Committee Act. Together, these obligations prolonged the panels' deliberations. Although the Antacid Panel completed its report in less than a year, more complex categories, containing more ingredients, occupied panels for several years, during which they may have met once a month.

The responsibility of producing a fully documented report required the panels to rely on FDA staff to assemble information, handle administrative and stenographic responsibilities, and often do much of the drafting. Thus, the sharp separation that existed between FDA's Bureau of Drugs and the NRC panels never characterized its relation with the over-the-counter panels. However, because discussions of draft reports were held in public meetings and panel members reached their judgments in these meetings, the fact that the final text and judgments represented their views, rather than those of agency staff, was clear. The assessments

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 8 of 48

of the panels generally have commanded considerable acceptance, because they were reached through public debate and were thoroughly documented.

At the outset of the review, FDA forecast that it would implement most of the panels' assessments. The agency has released the panels' recommendations in the form of notices of proposed rule-making, which are published in the Federal Register as the first step in translating them into regulations. The Bureau of Drugs has expressly reserved the privilege of disagreeing with a panel's findings either immediately or in a tentative final monograph, and it has sometimes done so. These occasions have been few, but usually controversial; and sometimes the Bureau has retreated from its initial disagreement. No manufacturer has been successful in overturning, administratively or in court, a panel judgment in which the Bureau of Drugs concurred.

Perhaps an even better measure of the credence given the panels' assessments is the high degree of voluntary compliance displayed by manufacturers. They have abandoned, albeit often reluctantly, most of the ingredients whose effectiveness the panels have doubted. Almost without exception, they have acceded to the panels' safety judgments. Similarly, they have generally accepted the panels' recommendations for changes in labeling. This remarkable commercial deference to scientific judgment has several explanations, in addition to the credibility of the panels. The slow pace of the review permitted manufacturers to make changes in their formulas or labeling without serious market disruption. The procedures of the panels themselves afforded opportunities for manufacturers to submit information and make arguments before a judgment was rendered. Perhaps as important, the panels' assessments, thus far, have not often jeopardized the continued marketing of major products or whole classes of drugs. If that occurs, it is likely that the panels' findings will encounter more determined opposition.

NATIONAL TOXICOLOGY PROGRAM PANEL ON FORMALDEHYDE

The National Toxicology Program (NTP) was established in 1978 by the Secretary of the Department of Health and Human Services to coordinate all toxicity testing of chemicals in the Department and to facilitate communication between the research and regulatory agencies. NTP

embraces the relevant toxicity testing activities of the National Cancer Institute, National Institute of Environmental Health Sciences, FDA (and its National Center for Toxicological Research), and the Centers for Disease Control. OSHA, EPA, and CPSC also participate in NTP. A major advisory group for NTP is its Executive Committee, which is made up of the heads of the agencies listed above, as well as the Director of the National Institutes of Health and the Assistant Secretary for Health. NTP thus serves as a vehicle for cooperation among the four regulatory agencies--FDA, EPA, OSHA, and CPSC--especially in recommending candidate substances for testing. At least one agency has also called on NTP to review risk assessments: the FDA has on two occasions asked another NTP advisory group--the Board of Scientific Counselors--to review the carcinogenicity data and the agency's analysis of those data on two color additives being considered for agency approval. In addition, NTP has served on one occasion as a structure through which a risk assessment of interest to all four regulatory agencies was performed.

In April 1980, CPSC (in cooperation with the Interagency Regulatory Liaison Group) requested that the NTP help to form an interagency panel on formaldehyde to review the carcinogenicity data on this chemical. The Panel consisted of 16 government scientists, most of whom were experts in toxicology, pharmacology, and epidemiology. Three of the IRLG agencies--EPA, FDA, and OSHA--also supplied scientists as members. Although no employee of CPSC was an official Panel member, a liaison representative of the agency attended all meetings and contributed to portions of the final report. In addition, CPSC personnel assisted the Panel by preparing bibliographies and handling arrangements.

The Panel on Formaldehyde thus serves as an example of a centralized assessment body that, although placed outside the agencies, maintained some association with the scientific staffs of each. The decision to confine the membership to government scientists was driven, in part, by a desire to avoid delays associated with compliance with the Federal Advisory Committee Act's requirements for establishing outside committees. The Panel's creation was viewed as an experiment in interagency coordination.

The Panel met three times. It generally deliberated in private, and its meetings were not announced. The Panel did consult with Chemical Industry Institute of Toxicology scientists who were responsible for designing

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 9 of 48

and conducting the carcinogenicity study being evaluated, and it permitted both oral and written statements from the Formaldehyde Institute, a trade association of users and manufacturers. Although the Panel reported its findings somewhat later than initially forecast by CPSC, the time required was a relatively brief 6-7 months. One unanticipated delay resulted from the necessity for a second review of the pathology slides from the major study being evaluated. The report stated that evaluation of the findings on carcinogenic effect and other related data convinced the Panel members that formaldehyde is an animal carcinogen when inhaled. This finding has been supported by many other scientists, and the Panel's report has since been published in a peer-reviewed scientific journal. The Panel also concluded that none of the available epidemiologic studies negated the inference that formaldehyde posed a cancer risk for humans. It did not attempt to estimate the risk of cancer for any exposed segment of the population. It did include, however, a quantitative dose-response assessment.

The NTP Panel's formation and performance demonstrate that such ad hoc collaboration is manageable and can function well. Despite the quality of its report and its timely production, however, the NTP Panel's deliberations and report have not yielded any regulatory efficiencies. In early 1982, CPSC banned further use of urea-formaldehyde foam insulation, in part on the basis of the Panel's report, as well as the agency's own risk assessments of formaldehyde's acute and chronic effects. In contrast, EPA has declined to initiate regulation of formaldehyde in response to the Panel's assessment. The Agency declined to act under Section 4(f) of the Toxic Substances Control Act, noting that the animal data available on carcinogenicity did not constitute a "reasonable basis to conclude that [formaldehyde] presents or will present a significant risk of serious or widespread harm to human beings from cancer. . . ." However, because the Agency's posture is equivocal and not clearly documented, the degree to which it relied on the Panel's assessment in reaching the conclusion is unclear.

Neither of the other two agencies followed CPSC's lead. OSHA declined to issue an emergency standard for worker exposure to formaldehyde, concluding that it poses no imminent hazard; and it recently announced that it was unable to proceed to establish a permanent standard, because the evidence of animal carcinogenicity did not

reveal what, if any, risk exposed workers might confront. These decisions were also based on OSHA's own assessment of risks, but the degree to which OSHA relied on the Panel's assessment for the agency's hazard identification step is unclear. Both EPA and OSHA are continuing to collect data on formaldehyde, but no regulatory action appears likely in the near future. FDA has not acted, because the potential formaldehyde exposures from agency-regulated products were judged to be very low.

The contrasting regulatory outcomes should not be interpreted as indicative that the Panel on Formaldehyde failed in its mission. Although the four agencies planned to consider its report carefully, the Panel's findings were not expected to be binding. Each agency remained free not only to fashion its own regulatory response on formaldehyde, but to qualify, or to dissent from, the Panel's determination of carcinogenicity and estimate of risk. Factors other than the Panel report's validity and utility are more likely explanations for the divergent agency responses. First, the Panel's report was submitted shortly before the 1980 national election, whose outcome forecast fundamental shifts in regulatory policy at EPA and OSHA. Second, the agencies confront exposures to formaldehyde that differ widely in character and intensity, yielding important differences in potential risk. Finally, the statutory criteria governing their decisions could plausibly lead them to accord different weights to the Panel's findings. OSHA, for example, had to decide whether formaldehyde posed a risk sufficient to justify emergency protective measures despite any costs of immediate action.

EPA'S USE OF SCIENTIFIC REVIEW PANELS

The EPA has had considerable experience with independent scientific panels, but they have served the Agency differently from the risk assessment panels discussed in the preceding section. EPA's panels typically have reviewed the work of Agency scientists and analysts, rather than perform their own risk assessments. Also, most panels serving EPA are mandated by Congress and play legally prescribed roles in the Agency's decision-making process. We examined two such panels: EPA's Scientific Advisory Panel and the Subcommittee on Airborne Carcinogens (a unit of EPA's Science Advisory Board).

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 10 of 48

EPA's Scientific Advisory Panel (SAP)

The Scientific Advisory Panel was established by Congress in the 1975 Federal Insecticide, Fungicide, and Rodenticide Act to review EPA's evaluations of the environmental and health risks posed by specific pesticide uses. Broadly speaking, the Panel reviews risk assessments prepared by EPA's Office of Pesticide Programs to support contemplated regulatory actions against hazardous pesticides. It also reviews the proposed and final forms of such actions. Consultation was initially required only when the Agency contemplated suspending or canceling a pesticide's registration or issuing general regulations governing pesticide registration. Cancellations and general pesticide regulations must be submitted to the Panel for review before they take effect. Suspensions of registration do not require prior review, but EPA must submit the underlying studies for review promptly after any suspension action. EPA must also submit for peer review the "design, protocols, and conduct of major scientific studies" conducted under the pesticide act. The following description reflects activities undertaken before September 1981.*

The Panel normally consists of seven members selected by the EPA Administrator from among six persons nominated by the National Institutes of Health and six nominated by the National Science Foundation. Until its last meeting in June 1981, the Panel generally met once a month. Topics covered during 1980 and 1981 are shown in Table III-7. The Panel does not set its own agenda, although the chairman may control the sequence and conduct of individual sessions. The risk assessments that the Panel reviews are selected by the two divisions (Hazard Evaluation and Special Pesticide Review) of the Office of Pesticide Programs that use its recommendations. Virtually all the scientific and exposure information available to the Panel is provided by the division whose assessment is being reviewed, although much of this information comes originally from the registrant of the product in question. Panel members necessarily accept the authenticity of the information provided, although they sometimes question its quality.

*Authorizing legislation expired in September 1981, and new legislation has not been enacted (as of December 1982).

TABLE III-7 EPA Actions Reviewed by the Scientific Advisory Panel (1980-1981)

A. Regulations under Section 25(a) of The Federal Insecticide, Fungicide, and Rodenticide Act

1. Final Rulemaking for Registering Pesticides in the United States, Subpart E, Hazard Evaluation: Wildlife and Aquatic Organisms
2. Proposed Rulemaking for Registering Pesticides in the United States, Subpart L, Hazard Evaluation: Nontarget Insects
3. Proposed and Final Rulemaking for Registering Pesticides in the United States, Subpart D, Chemistry Requirements: Product Chemistry
4. Final Rulemaking for Amendment of 40 CFR 162.31 by Adding Certain Uses of Eight Active Ingredients as Restricted Pesticides
5. Proposed Rulemaking for Registering Pesticides in the United States, Subpart M, Data Requirements for Biorational Pesticides
6. Final Rulemaking for Registering Pesticides in the United States, Subpart N, Chemistry Requirements: Environmental Fate
7. Informal Review of Draft Proposed Pesticide Registration Guidelines, Subpart K, Exposure Data Requirements: Reentry Protection
8. Review of Proposed Pesticide Registration Guidelines, Subpart H, Labeling of Pesticide Products
9. Review of Final Rule on Classification of 11 Active Ingredients for Restricted Use

B. Cancellations under Section 6(b) of the Federal Insecticide, Fungicide, and Rodenticide Act

1. Dimethoate
2. Diallate
3. Lindane
4. Strychnine
5. Ethylene dibromide
6. Oxyfluorfen (Goal 2E)
7. Wood preservatives, pentachlorophenol, creosote, arsenicals

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 11 of 48

Meetings are open to the public, and interested parties are generally encouraged to make presentations. These meetings sometimes focus on risk management issues, rather than on the health and environmental assessments submitted to the Panel, in part because participants making presentations are not confined to addressing scientific aspects of the Agency's risk assessments. Equally important in the consideration of nonscientific issues has been Congress's decision not to restrict the Panel to a strictly scientific review of the Agency's risk assessments. (The Panel's mandated review responsibilities extend to contemplated EPA actions that combine both risk assessment and regulatory policy elements.) Although the rationale for the Panel's creation was to introduce independent scientific review into EPA's deliberations, the mechanism chosen has routinely resulted in the Panel's commenting on the Agency's choice of regulatory options. The Agency has sought to anticipate the Panel's tendency to stray from the scientific issues before it and has attempted to frame specific questions on which comments are requested.

The participation of the Panel probably has improved the quality of EPA analyses and added to their credibility among both environmental and industry groups. However, expectations of some EPA critics that it would repudiate the Agency's scientific analyses have not been realized. Over the last 5 years, the Panel has agreed with most Agency risk assessments brought before it. There have been some notable exceptions, such as the Panel's disagreement with the Agency's handling of 2,4,5-T. The endorsement of most Agency assessments and Agency actions based on those assessments by the Panel have been extremely helpful in improving Agency credibility and rendered its actions less vulnerable to challenge in administrative or judicial hearings, as with the Panel's support of EPA action on wood preservatives. The Panel's success can be traced to several causes: its public deliberations, which may have made it difficult for EPA to ignore its comments; its continuity (until its authorizing legislation expired), which permitted it to understand EPA's approaches and simultaneously strengthened its influence with EPA staff; and the scientific distinction of individual Panel members.

In the case of EPA's decision to suspend use of 2,4,5-T and Silvex (its companion product) for some applications and to hold wide-ranging hearings on other applications, the Panel declined, after 3 days of public meetings, to support the Agency's proposed proceedings.

The Panel believed that additional data, including results of further tests for carcinogenicity and reproductive toxicity and of more complete monitoring for residues, were required before a hearing could be held profitably. Because EPA had not asked the Panel to approve the holding of a hearing and believed that it would be more efficient to deal with all uses of 2,4,5-T at one time, the Agency persisted and announced a hearing on the risks and benefits of 2,4,5-T, which began in March 1980. This difference, coupled with congressional displeasure with EPA's original suspension of 2,4,5-T and Silvex, led ultimately to the 1980 statutory amendment mandating that the Scientific Advisory Panel review the studies that underlie suspension decisions.

EPA's Subcommittee on Airborne Carcinogens

The Subcommittee on Airborne Carcinogens, a part of EPA's Science Advisory Board, was not mandated by statute. It was created in 1980 at the request of the Assistant Administrator for Air, Noise, and Radiation to review the assessments that the Agency is statutorily required to submit for Board review. Members of this Subcommittee were appointed by the Administrator; however, it no longer exists, having recently been merged with the Environmental Health Committee of the Science Advisory Board.

The Subcommittee reviewed six pairs of draft documents that included hazard identification and dose-response assessments produced by the Carcinogen Assessment Group and exposure assessments produced by private contractors for EPA's Office of Air Quality Planning and Standards. The chemicals evaluated in those documents were trichloroethylene, perchloroethylene, methylene chloride, methyl chloroform, acrylonitrile, and toluene. Subcommittee members reviewing these documents included a biochemist, a biostatistician, a pathologist, an engineer, an oncologist, a toxicologist, and a meteorologist. Five members were affiliated with universities and one with a research consulting organization; the seventh was a private consultant.

In accordance with the Federal Advisory Committee Act, the Subcommittee's review was held in public and announced in the Federal Register, and interested members of the public were invited to make oral and written presentations. Several such presentations were made, primarily by representatives of industries that would be affected

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 12 of 48

by EPA regulation of the substances under discussion. EPA and contractor personnel also attended the review and participated actively, briefing the Subcommittee on the contents of documents, answering members' questions, and defending their work against criticism.

The Subcommittee did not write a report after its review, and the absence of a summary report has led to some confusion regarding the nature of its criticisms. Review of the transcript of its second meeting (September 5, 1980) and discussions with various participants in that review meeting have revealed several general criticisms of the Carcinogen Assessment Group's risk assessments. One was that the documents provided to the Subcommittee were not sufficiently detailed; i.e., they did not provide enough scientific information from the various studies cited to permit the Subcommittee to make an independent assessment of the quality and validity of the studies. Another criticism raised by the Subcommittee was that the conclusions drawn did not reflect the quality of the data on which the risk assessments were based. Some Subcommittee members asserted that such considerations may, in fact, be precluded by rigid adherence to the Agency's guidelines for risk assessment.

Other criticisms focused on specific issues, including the validity of basing a conclusion of carcinogenicity on an increase in mouse liver tumors, the importance of contaminants in the test chemicals, and the wisdom of using a single model for extrapolating from high to low doses. The Subcommittee viewed these issues as primarily scientific, whereas Agency staff considered them, although resting on scientific principles, as resolvable through the choice of conservative policy options--a choice embodied in the Agency's guidelines. These differences between the Subcommittee and Agency staff emphasize the conclusion set forth in Chapter I that many components of risk assessment lack a firm scientific answer and require a judgment to be made. In some cases, such judgments may be informed by scientific arguments, but may ultimately rest on policy preferences. The difficulties in communication between the Agency and the Subcommittee also underscore the importance of explicit risk assessments and written reviews.

The differences reported above have not yet been fully resolved. The Agency's experience with the Subcommittee highlights some difficulties in using a review body that has not had sufficient time to develop a working approach to its task. It also emphasizes the importance of explaining Agency risk assessment procedures, including the adherence to specific guidelines, to review panels. Concerns similar to those of the Subcommittee have been expressed by members of the Environmental Health Committee, which replaced it, and Agency staff are currently considering changes in the risk assessment procedures embodied in their guidelines.

PROPOSED CHANGES IN ORGANIZATIONAL ARRANGEMENTS FOR RISK ASSESSMENT

Proposals to reform the organizational arrangements for risk assessment have been advanced to reduce perceived shortcomings in agency practices. The criticisms to which these proposals respond may be summarized as follows:

- Bias. Critics of agency performance suggest that decision-makers approach risk assessment with attitudes about regulation that preclude objectivity. Regulators, for example, may skew their assessment of risks associated with a particular substance to support a preference to regulate or not to regulate that substance.
- Exaggeration. This criticism is closely related to the first. The suggestion is that regulatory agencies, accustomed to operating in an adversary mode and expecting their judgments to be challenged in administrative hearings or in court, typically overstate the risks associated with hazards that they decide to regulate or understate the risks associated with hazards that they decide not to regulate. The instinct to support a position with every available argument may distort interpretations of scientific data, choice of extrapolation procedures, and assumptions about human exposure. The critical role of legal staff in preparing agency documents is thought to foster the adversarial style.
- Poor Public Understanding. If risks are misdescribed, it follows that public perception of the risks will be inaccurate. In addition, because agency announcements of regulatory actions typically stress the ultimate risk management strategy, such as the banning of saccharin, and do not explain why a particular action is being taken, the public is led to infer the degree of risk from the action proposed or from the decision not to act. However, an agency's ultimate decision may be dictated by statutory language or regulatory policies that emphasize considerations other than degree of risk.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 13 of 48

- Poor-Quality Personnel. This argument is straightforward, if unflattering. It is that regulatory agencies cannot attract or retain adequate numbers of highly qualified scientists to perform risk assessments. Many of their personnel are removed from active research by time and distance and are unfamiliar with the latest developments in their fields.
- Inconsistency. This criticism supports proposals for centralization of risk assessment. To the extent that separation is a prerequisite to centralization, this criticism would also support institutional separation. The suggestion is simply that agencies have applied inconsistent criteria and reached inconsistent results in assessing the risks posed by the same hazards. Such inconsistency is more likely when each agency is responsible for performing its own assessment.
- Redundancy. Starting from the assumption that different regulatory agencies have been, and are likely often to be, concerned with the same hazards, the critics argue that current arrangements force government regulators, affected industries, and interested scientists to deal with litigation on the risks of a given substance several times. Accordingly, a central institution responsible for performing risk assessments for all agencies might yield process efficiencies and reduce costs for all participants.

DESCRIPTION OF PROPOSALS

The central proposals for changes in institutional arrangements for risk assessments developed by the Office of Science and Technology Policy (OSTP) and the American Industrial Health Council (AIHC) and presented in H.R. 638 have sparked much of the current debate and precipitated this study. For several years before, however, dissatisfaction had been expressed with the procedures by which government bodies used scientific data and resolved what purported to be scientific issues. This dissatisfaction led to one of the precursors of the current proposals: the idea of a science court for resolving scientific issues underlying regulatory decisions. That suggestion and other, more recent proposals for procedural and structural reforms are discussed briefly below. The primary objective of this section, however, is to facilitate evaluation of the three main proposals that inspired this study.

Science Court

An important precursor of the OSTP proposal was the science court concept of Kantrowitz (1975). The science court was proposed to assist decision-makers with disputed scientific aspects of a decision. Hence, a basic premise of the science court is that it is both possible and desirable to separate the scientific elements of a public-policy decision from social and political considerations. The judges of a court were to be impartial, competent scientists from relevant disciplines who were not involved in the dispute. These judges would hear testimony from scientific experts on both sides of the issue, who would be allowed to cross-examine each other. The rationale was that scientist advocates are best qualified to present their own cases and to probe the weaknesses of their opposition. In the environment created in such a court, complete objectivity would be neither assumed nor necessary. After hearing all witnesses, the judges would issue a summary of their opinion of the meaning of the scientific evidence. Their opinions would deal only with scientific questions and could not include recommendations for public policy. Many details of a science court's procedures and operations are, however, unclear. Even after several years of sometimes heated debate in the scientific and regulatory communities, the overall reactions to the concept can be characterized as at best only lukewarm. Although a genuine science court will probably not be established, the underlying idea of separation of scientific issues from social and political considerations in decision-making has since appeared in other proposals.

FDA's creation and use of public boards of inquiry is the nearest analogue to the science court that has been put into practice. In 1975, FDA, on its own initiative, adopted regulations describing a public board of inquiry, a new kind of decisional body that could substitute for the traditional trial type of hearing before an administrative law judge if parties to formal disputes before the agency could agree. A board of inquiry is an ad hoc panel of three independent scientists, qualified in relevant disciplines, who hear evidence and arguments and render a preliminary decision, which may be appealed (like that of an administrative law judge) to the Commissioner of FDA. The procedure assumes that disputes that are primarily scientific can be resolved more accurately, faster, and with greater credibility by an

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 14 of 48

expert tribunal. FDA's novel procedure has been tried only once, to resolve safety issues concerning aspartame, a new artificial sweetener. This experience yielded, at best, equivocal support for the new procedure. Perhaps because of its novelty, the process took over a year to complete. The parties disagreed at length over the makeup of the board, the objectivity of its members, and the procedures it should follow. The FDA Commissioner ultimately rejected the board's conclusion that aspartame should not be approved and issued an opinion that both questioned the board's scientific rationale and corrected its interpretation of the legal criteria for approval of food additives. Other regulatory disputes, including FDA's refusal to approve the injectable contraceptive, Depo-Provera, are scheduled to be heard by boards of inquiry.

OSTP Proposal

A 1978 report from OSTP gave impetus to emerging proposals for separation and centralization of scientific aspects of risk assessment. The report recommended several steps to ensure consistency in the identification, characterization, and assessment of potential human carcinogens. Two interrelated stages in regulatory decision-making were delineated: Stage I, identification of a substance as a potential human carcinogen, qualitative and quantitative characterization of the risk it poses, and explication of the uncertainties; and Stage II, evaluation of regulatory options and their consequences. This dichotomy closely parallels our own distinction between risk assessment and risk management. The OSTP report recommended that a uniform decision-making framework be used in all agencies and that Stage I and Stage II functions be separated within or outside regulatory agencies while sufficient linkages were maintained to ensure relevance and timeliness. Such organizational experiments as the Carcinogen Assessment Group in EPA were highlighted. The report also suggested that the then-fledgling National Toxicology Program might eventually assume an expanded role in coordinating or overseeing some risk assessments for the regulatory agencies.

H.R. 638 and the AIHC Proposal

The 1978 OSTP report was a broad statement of principles. Two detailed proposals to create new risk assessment institutions have since been advanced. Because these proposals have several features in common, but also present important contrasts, they are summarized together (Table III-8).

In February 1980, Representative William Wampler first introduced legislation (U.S. Congress, 1981c) to establish a National Science Council. H.R. 638 calls for the creation of a new panel of scientists, entirely independent of the regulatory agencies, that would decide disputed scientific issues posed by regulatory initiatives. The AIHC had previously (1979) advanced a similar proposal to create an expert science panel that would evaluate the hazards of chemicals considered for regulation. Both proposals stress the importance of uniform, consistent resolution of the scientific questions underlying regulatory decisions. Both espouse the separation of risk assessment from the design and selection of regulatory responses, and both would use independent scientific experts to perform the assessments.

There are some basic differences between the two proposals. Under H.R. 638, any party could request referral of scientific issues to the National Science Council. The AIHC proposal specifies that, although any party may request a review, only federal agencies or Congress would have the authority to initiate mandatory review of scientific questions by the central science panel. H.R. 638 would apply only in formal adjudications. The AIHC proposal would apply to any agency proceeding in which risk assessment was at issue. Because rule-making is the primary mode for regulating hazardous substances, the AIHC proposal would apply to more regulatory actions than would H.R. 638. Under H.R. 638, decisions of the National Science Council would be binding on regulatory agencies. In contrast, assessments of the AIHC's science panel would not bind the agencies, but would carry a presumption of validity, subject to rebuttal in later regulatory proceedings.

The risk assessment bodies contemplated by the two proposals also differ in composition and procedures. The National Science Council would be a standing body of 15 full-time voting members serving 2-year terms. Individual chemicals would be assessed initially by advisory panels made up only of Council members. Each panel would have

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 15 of 48

TABLE III-8 Comparison of Major Features of H.R. 638 and the AIHC Proposal

H.R. 638	AIHC Proposal
Structure: Single continuing panel separate from agencies; centralized	Single continuing body with rotating members; in the NAS[a]
Membership: 15 full-time members appointed by chairman of NSB[b] from NAS nominees; members to be qualified, distinguished scientists	15 part-time members selected according to NAS procedures; members to represent the best scientists
Scope: Referral by any party of adjudications involving harm to human health from substances considered by CPSC, FDA, USDA,[c] DHHS,[d] OSHA, and EPA	Referral by any party or agency (only latter require mandatory consideration) concerning proposed rules or agency adjudications; all agencies with regulatory jurisdiction would be affected
Functions: Panel could prepare an independent risk assessment; its decision would be binding on the agency	Panel could prepare an independent risk assessment; its findings would be advisory, but would be part of record
Public Participation: Parties to adjudication would be involved	*Federal Register* notice of referral would solicit submission of data by public
Implementation: Legislation	Legislation

[a]National Academy of Sciences.
[b]National Science Board.
[c]U.S. Department of Agriculture.
[d]Department of Health and Human Services.

at least five voting members. The AIHC science panel would be established under the umbrella of the National Academy of Sciences and consist of 15 part-time members who would serve for terms of 3 years. The panel could establish working groups, which could be composed largely of outside experts. These divergent approaches to placement and composition of the panels and terms of members reflect different expectations about which status would attract the best scientists and perhaps about the extent to which the results would be binding. For example, the AIHC proposal assumes that distinguished academic and industry scientists would be unwilling to serve on a full-time basis for any substantial period.

Under H.R. 638, the National Science Council would decide scientific questions after conducting a formal "hearing on the record," in which all parties to the agency proceeding could participate. Under the AIHC proposal, referral of scientific issues to the panel would be announced, and the submission of written evidence and arguments would be invited. The less formal procedures visualized by the AIHC are consistent with its objective of obtaining nonbinding expert judgments on scientific issues that underlie decisions.

The two proposals embody different expectations as to speed of response. H.R. 638 would require the National Science Council to make a final report to the referring agency within 90 days of receiving a dispute. The AIHC proposal, however, imposes no time limits on the panel's assessment, except that the panel "operate expeditiously but not precipitously" (Higginson, 1982).

Single-Agency Proposals

H.R. 638 and the AIHC proposal espouse government-wide reform of the institutional means for risk assessment. Other notable recommendations for institutional restructuring have been addressed to individual agencies or agency programs. In 1981, for example, Senator Orrin Hatch introduced legislation (U.S. Congress, 1981d) to amend the food-safety provisions of the Federal Food, Drug, and Cosmetic Act. His bill included a provision permitting FDA to request, or affected third parties to demand, assessment of the risks associated with specific food constituents, with such assessment to be performed by a panel of scientific experts appointed by the National Academy of Sciences. The panel's assessment would be

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 16 of 48

advisory, rather than binding on the agency. Similar provisions have appeared in other proposals to revise government regulation of food safety, including a proposal developed by the Food Safety Council (1979). These proposals appear to share assumptions underlying the AIHC proposals: that agency risk assessments cannot be assumed to be objective, thorough, or expert and that an independent review should be available before a final decision is made. These proposals for independent scientific panels differ from H.R. 638 in three important ways: they would apply to one agency or program; they contemplate only an advisory role, rather than a resolving function, for the scientific panel; and they would apply to any agency proceeding in which risk assessments were at issue. The proposals thus can be viewed as agency- or program-specific illustrations of the AIHC proposal to create one central scientific panel to serve all agencies.

One such single-agency proposal has been adopted. In 1981, Congress amended the Consumer Product Safety Act (U.S. Congress, Omnibus Budget Reconciliation Act, 1981a) to require CPSC to consult with an ad hoc chronic hazards advisory panel whenever it contemplates rule-making concerning a product believed to pose a risk of cancer, birth defects, or gene mutation. A panel will consist of seven members appointed by the Commission from among 21 scientists nominated by the President of the National Academy of Sciences. Nominees may not be employees of the government or have any financial ties to any manufacturer or seller of consumer products. Each nominee must have "demonstrated the ability to critically assess chronic hazards and risk to human health presented by the exposure of humans to toxic substances or as demonstrated by the exposure of animals to such substances." The panel's responsibility is to prepare for the Commission a report on the substance that the agency is considering regulating. The panel is to review the scientific data and other information related to the substance and "determine if any substance in the product is a carcinogen, mutagen, or teratogen." The panel will also "include in its report an estimate, if such an estimate is feasible, of the probable harm to human health that will result from exposure to the substance." The Act requires that a panel submit its report within 120 days of convening, unless the Commission allows it additional time. A panel's report "shall contain a complete statement of the basis for its determination." The Commission must consider the panel's report and incorporate its evaluation into any advance

notice of proposed rule-making and any final rule. Apparently, the agency is not bound by a panel's determination of carcinogenicity or its estimation of the risk associated with exposure. Although it appears that each panel is to perform its own risk assessment, the statute is silent on the role to be played by agency staff and on the weight that a panel might legitimately accord to analyses prepared by the agency itself. These panels are exempted from the Federal Advisory Committee Act; the exemption presumably means that they are not required to provide advance notice of their meetings or to deliberate in public. A panel may seek information from third parties, but only through CPSC.

CRITICISMS OF PROPOSALS FOR SEPARATION AND CENTRALIZATION

The four federal regulatory agencies have responded skeptically to proposals to separate and centralize the function of assessing the risks of chemicals that are candidates for regulation (U.S. Congress, 1981b). Other observers have also found flaws in the proposals. A central criticism made by those who argue against full organizational separation between risk assessment and regulatory policy-making is that simply separating risk assessment from the regulatory agencies would not separate science from policy. This argument is based on the fact that the risk assessment process requires analytic choices to be made that rest, at least in part, on the policy consideration of whether to be more or less conservative when determining possible public-health risks. A second point is that, although extra-agency separation of risk assessment may help to minimize the influence of risk management considerations on this process, the agency responsible for deciding what exposure to permit or what costs to impose must make what is ultimately a political judgment based on the extent of risk determined in the risk assessment and often on the benefits and costs of regulatory action and its feasibility and political acceptability. For its decision to be politically acceptable and the decision-maker accountable, the agency must have responsibility for each of these components of regulatory decision-making. A third argument against institutional separation is related to the internal process by which agencies reach decisions. It is claimed that this process is unavoidably an iterative one. Different specialists are called on repeatedly for analysis and advice as an agency

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 17 of 48

identifies and considers new control options in attempting to reach a decision. Although this description may overstate the fluidity of internal agency deliberations, it captures something of their ad hoc character. Closely coupled with this argument is the necessity for agencies to retain scientific capability so that they can understand what a risk assessment means and how to use it in developing risk management strategies. Thus, even if risk assessment were performed outside the agency, a scientific staff representing many different disciplines would still be required, to ensure that an assessment would be interpreted and used correctly.

Other criticisms of proposals for risk assessment by a centralized panel stress the logistic difficulties of meshing independent risk assessment activities with the internal workings of different agencies. Experience suggests that it will be difficult for any risk assessment body to meet even generous time limits. Thus, agency decisions will probably be delayed by a requirement to consult, or refer issues to, such a body. A central panel also might become overburdened and cause additional delays. Critics of H.R. 638 and the AIHC proposal challenge the assumption that the regulatory agencies have reached inconsistent conclusions in evaluating various chemicals. The recent differences in the regulation of formaldehyde constitute a rare example of disparate treatment of the same chemical, and even this disparity may not betray basic disagreement over the interpretation of scientific data, as distinct from the degree of risk that justifies regulation. In the past, the agencies have often selected different control options or imposed different exposure limits for a given chemical, but these disparities have typically reflected differences in exposure (and thus in risk characterization) or differences in regulatory policy or statutory or administrative requirements; none of the current proposals addresses such differences.

CONCLUSIONS

The Committee was asked by the Congress to consider "the merits of an institutional separation of scientific functions of developing objective risk assessment from the regulatory process of making public and social policy decisions and the feasibility of unifying risk assessment functions." In this chapter, the Committee has addressed

these two issues and a third, related issue: the value of independent scientific review of agency risk assessments.

In its review, the Committee was sensitive to a number of considerations, including the scientific quality and regulatory relevance of the assessments performed. It also tried to ascertain how scientific and policy considerations were handled in the performance of risk assessment. To reach its conclusions, in the absence of accepted criteria for evaluating agency practices and proposals for change and in view of the sparseness of relevant empirical data, the Committee has relied on discussions with other persons knowledgeable and experienced in risk assessment activities, the limited available literature, and especially its own knowledge and experience in regulatory-agency risk assessments, as well as its review and analysis of past agency practices.

VALUE OF INSTITUTIONAL SEPARATION

1. Although organizational separation may help to ensure that risk management considerations do not influence the conduct of risk assessment, the degree of organizational separation that is optimal for individual agencies cannot be determined on the basis of the Committee's review.

Regulatory programs differ substantially in their degree of organizational separation. In the cases of NIOSH assessments that in the early 1970s were adopted by OSHA and NRC assessments relied on by agencies, the assessment function has been outside the regulatory agencies. At EPA, the risk assessment units in the Office of Health and Environmental Assessment of the Office of Research and Development prepare assessments for regulatory program offices that are organizationally under different assistant administrators. However, the Office of Toxic Substances does its own assessments, and several other program offices are responsible for their own exposure assessments. The risk assessments for the FDA'S Bureau of Foods are produced within the Bureau, but by an office distinct from offices responsible for formulating regulations and enforcement; since 1976, the Directorate of Health Standards Programs in OSHA has both performed risk assessments and formulated all early risk management options. Different agencies also have success-

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 18 of 48

fully used different organizational arrangements for risk assessment. FDA, for example, has often called on NRC and NTP for assessments, but in other cases relied on its own staff. The Committee's review of different agency structures and procedures did not demonstrate that one particular structure produced risk assessments of superior quality and integrity. In addition, the Committee notes that, even if there were a clear finding that a particular arrangement works for a given agency or program, it would be extremely difficult (given the diversity in agency and program mandates, personnel needs, and histories) to justify a suggestion that that arrangement would best serve all agencies or programs.

2. Organizational separation has several important drawbacks that are likely to be intensified with increasing degrees of separation.

There are several arguments against organizational separation. Separation of the risk assessment function from an agency's regulatory activities is likely to inhibit the interaction between assessors and regulators that is necessary for the proper interpretation of risk estimates and the evaluation of risk management options. Separation can lead to disjunction between assessment and regulatory agendas and cause delays in regulatory proceedings. Common sense suggests that increased separation would aggravate these drawbacks. In its review, the Committee observed these disadvantages when assessors and regulators were in different organizations (e.g., NIOSH and NRC). Another perceived drawback in extra-agency separation that was neither detected nor likely to emerge in the Committee's review is the erosion of scientific competence within agency staffs if risk assessments are routinely performed outside the agency. Also, any major organizational change may have a disruptive effect on agency performance; thus, such organizational changes are especially questionable when the benefits, if any, are unclear.

3. Organizational arrangements that separate risk assessment from risk management decision-making will not necessarily ensure that the policy basis of choices made in the risk assessment process is clearly distinguished from the scientific basis of such choices.

If risk assessment as practiced by the regulatory agencies were pure science, perhaps an organizational separation could effectively sharpen the distinction between science and policy in risk assessment and regulatory decision-making. However, many of the analytic choices made throughout the risk assessment process require individual judgments that are based on both scientific and policy considerations. The policy considerations in risk assessment are of a different character from those involved in specific risk management decisions and are generally common to all assessments for similar health effects. Thus, even when one has drawn the relatively obvious distinction between risk assessment and risk management, there remains the more difficult task of distinguishing between the science and policy dimensions of risk assessment itself. We believe that the latter distinction cannot be ensured or maintained through organizational arrangements. Given the inherent mixture of science and policy in risk assessment, organizational separation would simply move risk assessment policy into a different organization that would then have to become politically accountable. The Committee believes that other approaches are more likely to maintain the distinction between science and policy in risk assessment, most notably the development of and adherence to guidelines.

VALUE OF CENTRALIZATION

4. Common risk assessments performed primarily by scientists from all interested agencies on an ad hoc basis may capture the major advantages of centralization without the drawbacks that accompany permanent, extra-agency centralization.

An argument often advanced for centralization is that it might expedite and perhaps reduce the administrative costs of decision-making when two or more agencies contemplate regulation of the same substance. And if two or more agencies are going to regulate the same substance, there is much to be said for developing a system that facilitates production of a single, common risk assessment. This was one rationale for CPSC's decision to empanel a group of scientists to evaluate the carcinogenicity data on formaldehyde, and it argues in support of the central panels suggested in H.R. 638 and the American Industrial Health Council's proposal. Although the Com-

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 19 of 48

mittee endorses government-wide consistency in risk assessment, it is less sanguine concerning the prospects of a permanent arrangement for such centralized risk assessment as contemplated by these proposals, in which the idea of centralized assessment is inextricably linked to extra-agency separation. The Committee concluded that extra-agency separation would have disadvantages that would offset any advantages.

The Committee did find, however, that agency scientists could collaborate to perform joint risk assessments on an ad hoc basis. Because agency scientists would perform an assessment, such an arrangement would avoid most of the drawbacks of extra-agency separation. The Committee looked at the Panel on Formaldehyde as an example of a centralized assessment group. In the Committee's view, the Panel functioned well and produced an assessment that has been accepted by the scientific community. The Panel's assessment has not produced parallel regulatory action among the agencies, and the Committee observed that similar risk assessments should not necessarily lead to similar regulatory decisions, which reflect considerations that often justify different risk management responses.

USE OF SCIENTIFIC REVIEW PANELS

5. Independent scientific review of agency risk assessments improves the scientific quality of the assessments and strengthens them against later challenge.

Agencies and programs with mandated peer review panels, such as EPA's Office of Pesticide Programs, which is required to submit to a Scientific Advisory Panel proposals to cancel or restrict pesticide use, produce final risk assessments in support of regulatory decisions that are generally of high scientific quality and are accepted by the public and the regulated parties. In contrast, the Committee found several cases in which mechanisms for peer review could be markedly improved: OSHA, which uses public comments to refine its risk assessments, rather than formal peer review; NIOSH, which has not had a mechanism to ensure that reviewers' comments are given appropriate consideration; and FDA's Bureau of Foods, which uses ad hoc panels to review its assessments (a procedure that unfortunately can be circumvented).

- Standing and continuing review panels that have mechanisms to maintain the independence of their members appear to be the most useful review bodies.

Continuity and independence of review panels help to ensure that such panels are sensitive to regulatory needs while retaining the necessary scientific objectivity. Examples of standing committees, such as the Scientific Advisory Panel in EPA, support this perception. Conversely, the Committee observed that short-lived or ad hoc groups, such as the Subcommittee on Airborne Carcinogens, often do not have sufficient time to develop a working relationship among panel members and that much of the time allotted to review is actually spent in clarifying individual versus panel viewpoints and understandings. Similarly, an ad hoc panel may not clearly understand its role in relation to the regulatory process. Thus, standing panels appear to be of greater value to the agency than ad hoc committees. Furthermore, the existence of a standing panel might encourage an agency to seek its advice more frequently.

Because it is important for review committees to be free to express their scientific judgments without concern for regulatory implications, panels that are formed in a manner that neither compromises nor appears to compromise their independence are more likely to improve ultimate risk assessments. The Committee observed that several review panels used by EPA already have a nomination process that places the responsibility for developing a slate of possible panel members outside the agency. Although the EPA Administrator makes the final selections of panel members, the fact that nominations come from outside the agency emphasizes the intent that EPA panels be independent and as free of agency influence as possible. A related point is that membership on EPA panels, and in fact on most review panels used by the regulatory agencies, rotates; members are usually selected for staggered, fixed terms (generally 3-4 years). This rotation itself reduces the likelihood that members will develop an institutional bias.

- Review panels are best qualified to give scientific advice when they are composed of scientists who are highly knowledgeable in the appropriate disciplines.

For carcinogenicity risk assessments, for example, some relevant disciplines would be toxicology, pathology, biostatistics, chemistry, and epidemiology. The Com-

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 20 of 48

mittee believes that professional or organizational affiliation should not be used as a primary criterion in the determination of the makeup of a particular panel. That is, in contrast with the advisory panels used by OSHA, which are constituted to reflect balance among different affiliations and presumed biases, the Committee believes that scientific competence must be the primary factor determining panel membership if review panels are to be asked to give their advice on the scientific aspects of an agency's risk assessments. However, the Committee notes that panel members who understand the policy implications of their scientific judgments are more likely to be helpful to an agency's assessment process and that an attempt to balance viewpoints of scientifically qualified panel members may increase a panel's credibility.

- Review panels will be most effective if they have the authority to review agency risk assessments before announcement of the agency's intended regulatory actions, except in cases of emergency.

The Committee believes that review panels serving regulatory agencies should serve in an advisory capacity. That is, the judgments of a panel should not be binding on the agency. Nevertheless, the Committee also believes that the authority of agency review panels should be such that agencies must demonstrate that adequate consideration has been given to reviewers' judgments, and prior consultation with review panels helps to ensure this. Because announcements of intended actions or proposed regulations must be thoroughly developed and substantiated, review at the time of announcement or later is likely to be too late to influence an agency; although the regulation is only proposed, the decision of whether to act has, for all practical purposes, already been made. In the Committee's judgment, exceptions to this idea of prior review are appropriate in the case of emergency actions, such as suspension of pesticide registration. Risk assessments supporting such actions could be reviewed after the announced action.

- Independent panels with authority to review risk assessments for all agency regulatory decisions, including decisions not to act, are more likely to ensure that agency decisions rest on valid scientific grounds.

Panels with the authority to request the review of any agency risk assessment supporting a particular regulatory

decision will have a greater impact on agency decision-making. For example, if a panel can review only assessments referred to it by an agency, some agency decisions might not benefit from independent review of their scientific basis. This is especially likely if an agency has decided not to regulate. Such a decision may have considerable impact and should receive the same careful review as decisions to regulate. In addition, panels with the authority to request reviews can respond to suggestions for review from the public.

- Although most requirements of the Federal Advisory Committee Act are salutary, others may inhibit agency use of review panels.

The Committee believes that most provisions of the Act are beneficial and endorses such provisions as the requirement that advisory committees meet in public and provide advance notice of their meetings. However, the Act does impose requirements, some burdensome, for agency-created bodies that meet the definition of advisory committee. Notably, the Act requires that an advisory committee be formally chartered by an agency head and approved by the General Services Administration. This procedure has often proved cumbersome. Some agencies, such as FDA, lack independent chartering authority and thus require approval at the departmental level. In addition, procedures used by the General Services Administration for screening new committees have often imposed long delays, sometimes inspired by political concerns about committee membership or by resistance to the creation of new government "agencies." These legal requirements of the Act have caused some agencies to seek other ways of obtaining the views of scientific experts, especially when the issues involve single chemicals or tests. In such cases, regulators often confine their consultations to government scientists, who can be accessible immediately and, if necessary, for extended periods.

- Written reviews help to ensure agency consideration of scientific criticism.

A summary of a panel's review that is transmitted in written form and made available to the public will help to avoid confusion and to ensure agency consideration of the panel's comments. As mentioned earlier, in the absence of adequate mechanisms to ensure agency consideration of reviewers' comments, the comments might be

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 21 of 48

ignored, or the public might perceive that they are ignored. Putting its summary in writing should also ensure that the panel states its findings clearly and make it more likely that the agency will interpret its comments correctly.

OTHER OBSERVATIONS

6. Preparation of fully documented written risk assessments that explicitly define the judgments made and attendant uncertainties clarifies the agency decision-making process and aids the review process considerably.

When a fully documented written risk assessment is not produced before an agency's decision to regulate or not to regulate, it is difficult to understand the process by which an agency made its assessment. The Committee believes that the creation of such a document encourages public understanding of and respect for agency procedures and provides a basis for review by a scientific advisory panel. Furthermore, a detailed risk assessment document that clearly identifies the inference options chosen in the assessment and explains the rationale for those choices will help to maintain a sharper distinction between science and policy in the assessment of risk and will guard against the inappropriate intrusion of risk management considerations.

REFERENCES

AIHC (American Industrial Health Council). 1979. Recommended Framework for Identifying Carcinogens and Regulating Them in Manufacturing Situations.

EPA (Environmental Protection Agency). 1976. Health risk and economic impact assessments of suspected carcinogens: interim procedures and guidelines. Fed. Reg. 41(102):21402-21405.

EPA (Environmental Protection Agency). 1979. Water Quality Criteria, Request for Comments. Fed. Reg. 44(52):15926.

EPA (Environmental Protection Agency). 1980. Water Quality Criteria Documents; Availability. Fed. Reg. 45(231):79350-79353.

Food Safety Council. Social and Economic Committee. 1979. Principles and Processes for Making Food Safety Decisions. 54 pp.

Higginson, John. 1982. Report of the Scientific Workshop on the Critical Evaluation of Proposals by the American Industrial Health Council to Strengthen the Scientific Base for Regulatory Decisions.

Kantrowitz, Arthur. 1975. Controlling technology democratically. Am. Sci. 63:505-509.

NRC (National Research Council). 1981. The Handling of Risk Assessments in NRC Reports. A Report to the Governing Board, National Research Council, by the Governing Board Committee on the Assessment of Risk. 19 pp.

Office of Science and Technology Policy. 1978. Identification, Characterization, and Control of Potential Human Carcinogens: A Framework for Federal Decision-Making.

U.S. Congress. 1981a. Omnibus Budget Reconciliation Act. (P.L. 97-35, August 13, 1981) 15 U.S.C. 2077.

U.S. Congress. 1981b. House of Representatives, Committee on Agriculture, Hearings on the National Science Council Act, H.R. 638. Hearings Before the Subcommittee on Department Operations, Research, and Foreign Agriculture of the Committee on Agriculture, June 23, 1981.

U.S. Congress. 1981c. House of Representatives H.R. 638. National Science Council Act 97th Congress, 1st Session, 1981.

U.S. Congress. 1981d. Senate. S. 1442. Food Safety Amendments of 1981, 97th Congress, 1st Session, 1981.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 22 of 48

IV
Recommendations

The Committee has reviewed federal risk assessment for hazards to public health, particularly for chemically induced cancer, and has presented its findings concerning the nature of risk assessment, the nature and utility of risk inference guidelines, and the effects of alternative organizational arrangements on risk assessment. The Committee's review leads to the general observation that the process of risk assessment, as performed by and for federal regulatory agencies, has been developing rapidly in recent years, both with respect to its scientific basis and with respect to the agencies' organizational arrangements. Change this rapid is bound to lead to misunderstanding about the use of risk assessment in regulatory policy-making, particularly if some misconstrue risk assessment to be a strictly scientific undertaking. Much of the criticism of risk assessment stems from dissatisfaction with regulatory outcomes, and many proposals for change are based largely on the unwarranted assumption that altering the administrative arrangements for risk assessment would lead to regulatory outcomes that critics will find less disagreeable. Because risk assessment is only one aspect of risk management decision-making, however, even greatly improved assessments will not eliminate dissatisfaction with risk management decisions.

The Committee believes that the basic problem with risk assessment is not its administrative setting, but rather the sparseness and uncertainty of the scientific knowledge of the health hazards addressed. Reorganization of the risk assessment function will not create the data and underlying knowledge that assessors need to make risk assessments more precise. We hold that the most productive path to a solution has three parts:

- Implementation of procedural changes that ensure that risk assessments take full advantage of the available scientific knowledge while maintaining the diverse organizational approaches to administration of risk assessment needed to accommodate the varied requirements of federal regulatory programs.
- Standardization of analytic procedures among federal programs through the development and use of uniform inference guidelines.
- Creation of a mechanism that will ensure orderly, continuing review and modification of risk assessment procedures as scientific understanding of hazards improves.

The Committee offers in the following pages 10 recommendations whose implementation it believes will meet these general objectives.

IMPROVING RISK ASSESSMENT THROUGH PROCEDURAL CHANGES

RECOMMENDATION 1

Regulatory agencies should take steps to establish and maintain a clear conceptual distinction between assessment of risks and the consideration of risk management alternatives; that is, the scientific findings and policy judgments embodied in risk assessments should be explicitly distinguished from the political, economic, and technical considerations that influence the design and choice of regulatory strategies.

Although the Committee concludes that risk assessment cannot be made completely free of policy considerations, it also believes that policy associated with specific risk management decisions should not influence risk assessment unduly. Risk assessment and risk management involve different goals, kinds of expertness, and operating principles. The goal of risk assessment is to describe, as accurately as possible, the possible health consequences of changes in human exposure to a hazardous substance; the need for accuracy implies that the best available scientific knowledge, supplemented as necessary by assumptions that are consistent with science, will be applied. The ultimate aim of risk management is to evaluate tradeoffs between health consequences and other effects of specific regulatory actions; this evaluation includes the application of value judgments to reach a policy decision.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 23 of 48

Experience shows the difficulties that can arise from a blurring of the distinction between the two elements. If risk management considerations (for example, the economic or political effects of a particular control action for a particular chemical) are seen to affect either the scientific interpretations or the choice of inference options in a risk assessment, the credibility of the assessment inside and outside the agency can be compromised, and the risk management decision itself may lose legitimacy. Indeed, such consequences can flow from the mere perception, as well as the fact, of such influences. Each regulatory agency should commit itself to safeguarding the distinction between the processes of risk assessment and risk management. One among several suggestions for accomplishing this safeguarding is to restructure the formal organization, separating an agency's or program's risk assessment staff from its policy-making staff, possibly by establishing a separate risk assessment unit inside the agency. The Committee does not, however, recommend that agencies use any particular organizational arrangement for risk assessment. One might surmise that separating the staffs would help to reduce the likelihood that risk management considerations will influence risk assessment, but our survey of agency structures provided no clear evidence that such an influence was related to the degree of administrative separation.

Formal separation has disadvantages that must be balanced against its value in maintaining a distinction between risk assessment and risk management. Risk assessment and risk management functions are analytically distinct, but in practice they do--and must--interact. Organizational arrangements that completely isolate risk assessors from regulatory policy-makers may inhibit important communication in both directions. For example, to complete risk characterization, risk assessors must know what policy options are to be used to calculate alternative projected exposures, and new options may develop as the risk management process proceeds. Moreover, direct communication with the risk assessors is desirable to ensure that the regulatory decision-maker understands the relative quality of the available scientific evidence, the degree of uncertainty implicit in the final risk assessment, and the sensitivity of the results to the assumptions that have been necessary to produce the assessment. Such separation could also impair the risk manager's ability to obtain assessments that are timely and in a useful form. The advisability of organizational

separation hinges on comparison of its benefits and costs in particular agencies and programs.

Because drawbacks are likely to be most pronounced in the case of extra-agency separation, the Committee does not believe that it is appropriate to remove the risk assessment function and place it in an organization completely separated from the regulatory agencies, as is contemplated in the AIHC proposal and H.R. 638. This judgment is supported by the conclusion that the benefits of increased separation are uncertain and that the disruption and confusion caused by reorganization could be considerable.

Measures other than organizational separation can ensure the distinction between the assessment of risk and the consideration of risk management alternatives. These measures include the practice of preparing written risk assessments (Recommendation 2), arranging for independent peer review (Recommendation 3), and adhering to uniform guidelines for risk assessment (Recommendations 5 through 9).

RECOMMENDATION 2

Before an agency decides whether a substance should or should not be regulated as a health hazard, a detailed and comprehensive written risk assessment should be prepared and made publicly accessible. This written assessment should clearly distinguish between the scientific basis and the policy basis for the agency's conclusions.

Although agencies commonly perform risk assessments before they take regulatory actions, the written assessments that are prepared vary in coverage, amount of explanatory detail, format, and completeness to an extent that limits their use as instruments of communication. The Committee believes that the matters addressed are so important and the consequences so far-reaching that a written risk assessment should be prepared for every significant regulatory decision and that each should be a clear, detailed, and comprehensive account of the analysis performed. A written assessment should describe the volume and weight of scientific evidence to help to clarify the scientific and policy bases for regulatory decisions.

The written assessment should be made accessible to the public at a time and in a form that facilitates public participation in any attendant risk management decision.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 24 of 48

The Committee believes that the requirement to prepare a written assessment imposes a salutary discipline that, for several reasons, will improve the performance of risk assessment. First, the requirement to prepare a comprehensive written assessment will encourage the agency to explain how each component of the assessment was treated; that should minimize the likelihood that risk management considerations will, unnoticed, affect the outcome of the assessment. Second, a written assessment can help to distinguish the factual basis of a risk assessment from inferences drawn where there is a lack of scientific consensus; this distinction will facilitate scientific review of the risk assessment, document the scientific basis of the assessment for outside observers, and acquaint the regulatory decision-maker with the relative completeness of the scientific evidence. Third, it will aid communication among specialists working on different parts of the assessment. Fourth, the existence of an explicit description should simplify the conduct of later assessments of the same chemical, if additional scientific evidence comes to light or other regulatory programs review the same substance. Finally, written risk assessments will be useful to institutions that oversee regulatory agencies, notably Congress and those responsible for judicial review. It is important, however, that the format and scope of written assessments not become an independent basis for legal attack.

Content and Form

An agency's written risk assessment should set forth in detail the nature and quality of the relevant scientific evidence concerning the substance in question and should cover all relevant components of risk assessment. It should reflect attention to any applicable guidelines relied on in interpreting the evidence, so that a reader can ascertain what inference options were used, and should describe the scientific rationale for any departures from methods prescribed in such guidelines. If the choice of inference options is not governed by guidelines, the written assessment itself should make explicit the assumptions used to interpret data or support conclusions reached in the absence of data. The document should acknowledge gaps and uncertainties in available information.

An agency's written assessments are likely to prove most useful if they follow a consistent format, so that readers, once familiar with the format, can use them efficiently. We believe that each program or agency can establish a uniform structure for its written assessments, and we hope that similarity, if not uniformity, will be possible in written assessments prepared throughout the government.

Actions Covered

This recommendation is not intended to apply to the risk posed by every substance, use, or exposure that engages an agency's attention. It is intended to apply to agency decisions concerning important human exposure to a hazard. Such decisions would include (but not be limited to) establishment of an occupational safety and health standard by OSHA, cancellation by EPA of the federal registration of a pesticide to which there is widespread human exposure, and EPA promulgation of limits for an air or water pollutant. The categories of actions covered by this recommendation could be defined precisely only after detailed statutory analysis. EPA appears to have had satisfactory experience with the practice of classifying its regulations as "major" (those with very large economic and other effects that require an extensive regulatory analysis and formal review by the Office of Management and Budget), "significant" (a larger category defined by internal EPA criteria), and "minor" (a similarly large group of routine and technical actions). We suggest that EPA prepare a written assessment for every major and significant action, and we encourage other agencies to devise similar methods of identifying which regulatory actions require written assessments.

An agency's decision to refrain from regulation can often have important consequences, both for health and for the economy, and such decisions should rest on accurate, objective assessments of risk. The denial of a petition to act on a chemical to which exposure is extensive is an example. When an agency is confronted with choosing between limiting exposures to a substance and taking some lesser action and there is serious dispute over the character or extent of the risk posed, a written assessment is advisable.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 25 of 48

RECOMMENDATION 3

An agency's risk assessment should be reviewed by an independent science advisory panel before any major regulatory action or decision not to regulate. Peer review may be performed by science panels already established or authorized under current law or, in their absence, by panels created for this purpose.

- If an agency's workload is substantial, a standing advisory panel (or panels) should be established to review its risk assessments; otherwise, ad hoc panels should be established on a case-by-case basis.
- Panel members should be selected for their scientific or technical competence.
- The appointment of members should be the responsibility of each agency director, but nominations from the public and scientific organizations should be invited, unless current law prescribes another procedure.
- Panels should provide to the referring agencies written evaluations of agency risk assessments, and the evaluations should be available for public inspection.

This recommendation endorses outside peer review of agency risk assessments. Such review should contribute to the important distinction between risk assessment and risk management, because risk management information would be excluded from the review; should improve the scientific quality of the assessments through the process of criticism and response; and should increase the credibility of agency assessments. The practice of preparing written risk assessments will facilitate the review process.

The peer review function that we visualize is already evident in some agencies. We believe that a single approach would not fit all contexts, but that any mechanism for scientific peer review should meet the general criteria described below.

Panel Form

The review function we recommend could be performed effectively by an appropriately qualified standing panel of independent scientists that is responsible for reviewing agency assessments of a particular class of hazards. Any agency program responsible for a large number of

compounds to which humans are exposed in large amounts seems to be an appropriate candidate for a standing scientific review panel, but some programs may deal with so few chronic health hazards that a standing panel is not warranted. The Committee specifically contemplates that the review function recommended here can be performed by panels already available to several agency programs.

Panel Composition and Selection

Members of a scientific review panel should be selected for their competence in fields relevant to the assessment of risks of the kind being evaluated. In our judgment, employees of private business organizations, members of environmental groups, and government research or regulatory agency employees should not necessarily be disqualified; but no panel members should be employees of the agency whose risk assessments are to be reviewed, nor should any members participate in the review of substances in which they or their employers have substantial economic or other interests or on whose risks they or their employers have publicly taken a position. It is important to safeguard both the reality and the appearance of complete objectivity for each review.

We contemplate that, as is common for existing panels, the appointing official would be the head of the agency whose risk assessments are to be reviewed. Such an arrangement could be thought to jeopardize a panel's independence from the agency, particularly in cases in which it is known which chemicals the panel will review. Accordingly, each agency should establish procedures for obtaining nominees for panel membership whose objectivity is ensured. For example, some current procedures call for agency selection of members from lists of nominees provided by the President of the National Academy of Sciences and by the Directors of the National Institutes of Health and the National Science Foundation. We see no magic in any particular nomination process. The important objective is a process that, first, ensures that panel members are selected for their training and experience in relevant fields; second, prevents the appointing official from forming a panel that will produce (or appear to produce) a predetermined result; and, third, operates expeditiously. We recommend that this process include an opportunity for members of the public to nominate persons for panel membership.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 26 of 48

Panel Functions

Our recommendation contemplates that, in a typical case, the responsible agency will have prepared a written assessment of the risk posed by a substance. The independent scientific panel would be asked to review that assessment for comprehensiveness, scientific accuracy, and consistency with any applicable risk assessment guidelines. If such guidelines are flexible, an important panel function will be to ensure that departures from the inference options favored by the guidelines are justified on scientific grounds. In performing this role, the panel should, if it desires, have access to all the data available to the agency, including those on which the agency's analysts relied, as well as the agency's written assessment. The panel should subject the agency's risk assessment to such scrutiny as the members find necessary to satisfy themselves that it is, with or without revisions, as complete and objective as available data permit. The panel should provide a written evaluation of the agency's risk assessment, including recommendations for revision, if appropriate. This evaluation should be available for public examination by the time the agency initiates public proceedings to alter human exposure to the substance in question for example, when the agency issues a notice of proposed rule-making.

Panel Agenda

Independent review of agency risk assessments is designed to ensure the integrity and quality of the scientific bases for regulatory decisions affecting human health. Therefore, the Committee recommends that every action, including a decision not to regulate, that requires a written risk assessment be available for independent scientific review. A scientific review panel's agenda may also include risk assessments for other decisions of interest to panel members, or its review could be initiated after a request by a third party. In the latter case, panels should have the authority to decide whether or not to respond to such requests for review. In general, the Committee expects that the panels would exercise discretion in invoking their authority to review assessments for routine, minor actions.

Timing of Review

Independent scientific review of agency risk assessments should occur before an agency commences the public process leading to regulatory action. The purpose is to expose the agency's initial assessment of the risk posed by a substance to expert scrutiny at a time when review can influence the agency's course of action. Experience suggests that agencies are less receptive to criticism of the basis of their actions after they have announced a proposed course of action. Furthermore, although independent review can sometimes forestall misguided regulatory actions even after they are initiated, prior review of such actions may help to avoid serious damage to agency credibility and unnecessary costs to private interests that would be adversely affected by public proposals for regulatory action. We recognize an important exception to our general recommendation of preaction peer review. Several statutes expressly empower agencies to act in an emergency to curtail human exposure to a substance that poses a serious health risk. Agencies have also devised informal procedures to effect immediate protection of humans exposed to dangerous substances in other contexts. Our recommendation is not intended to cast doubt on the legitimacy of such authority or to impede its appropriate exercise. When an agency concludes that a hazard warrants immediate regulatory action to limit human exposure, it should be able to take action consistent with existing law without first going through the review process that we recommend. Promptly thereafter, however, the agency should submit its written risk assessment for independent review in accordance with the procedures outlined here.

Weight of Panel Evaluation

A scientific review panel's critique of an agency's risk assessment should not be binding; that is, the agency should not be obliged to revise its risk assessment if the panel regards it as deficient. Agencies have a responsibility to state the basis of their actions, and the authority for their actions must remain their own. Serious panel criticism, however, would in practice cause any agency at least to reconsider, and ordinarily to revise, its risk assessment. The agency should discuss any important criticisms of its assessment in its proposed regulatory action, and its response to a panel's criti-

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 27 of 48

cisms would be an appropriate subject for public comment, as well as a possible basis for judicial challenge to any final action.

We believe that an important benefit of peer review occurs before the review begins: risk assessors who expect an assessment to be subjected to serious scrutiny by eminent qualified reviewers are likely to be more careful and clear about the use and limits of scientific evidence.

Federal Advisory Committee Act

The Federal Advisory Committee Act imposes many salutary requirements on panels established to advise federal agencies, including notably the requirement that panel meetings be held in public. But the Act's requirement that new advisory committees be chartered by the General Services Administration imposes substantial delays and its requirement that panel meetings be announced in the Federal Register at least 15 days in advance can markedly slow a panel's work. Consideration should be given to modifying both requirements or exempting such panels from the Act, as Congress did for CPSC's Chronic Hazard Advisory Panels.

RECOMMENDATION 4

When two or more agencies share interest in and jurisdiction over a health hazard that is a candidate for regulation by them in the near term, a joint risk assessment should be prepared under the auspices of the National Toxicology Program or another appropriate organization. Joint risk assessments should be prepared primarily by scientific personnel provided by the agencies and assisted as necessary by other government scientists.

This recommendation endorses coordination in assessing the risks of chemicals that are likely candidates for regulation by two or more agencies. Although all the end uses of a substance may fall within the jurisdiction of one agency (such as FDA for a food additive), exposures occurring during production, transportation, and distribution usually are within other agencies' jurisdictions. Thus, chemicals that pose a hazard to human health are at least theoretically subject to regulation by two or more

federal agencies. The Committee agrees with proponents of the centralization of risk assessment responsibilities that the agencies involved should operate on the basis of a common assessment of the substance's risks. However, the Committee differs with respect to the method for achieving this end.

Actions Covered

Our recommendation does not call for the performance of a joint risk assessment in every instance in which a substance potentially falls within the jurisdiction of two or more agencies; we limit our proposal to circumstances in which assessment by more than one agency is likely in the near future. This limitation has two rationales. First, substantial risk may be associated with routes of exposure of concern to only one agency. Under such circumstances, it would be unreasonable to invest time and resources to establish an interagency panel of scientists. Second, even if different types of exposure entail risks, a substance may legitimately rank low in priority for one agency and high for another.

Placement and Procedures

The approach we visualize is similar to that followed in 1980, when the Interagency Regulatory Liaison Group, at the suggestion of CPSC, sought the assistance of the National Toxicology Program to examine the carcinogenicity of formaldehyde. The Program formed an ad hoc panel that consisted entirely of government scientists, including some from EPA, OSHA, and FDA.

We suggest that the National Toxicology Program be the usual vehicle for coordinating preparation of joint risk assessments. The National Toxicology Program has been in operation for several years and, in the Committee's judgment, has performed capably as coordinator of federal toxicologic research. It has displayed an ability to command the service of the government's best scientists. And it has developed effective working relationships with the regulatory agencies, which have become accustomed to looking to it for assistance in evaluating substances that are candidates for regulation.

We expect that suggestions for establishment of an interagency task force to evaluate a hazard will come

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 28 of 48

from the interested regulatory agencies. The personnel assigned to assemble the relevant data and perform the assessment could include scientists from the interested regulatory agencies, including the initiating agencies, and scientists from government research organizations, such as the National Institute of Environmental Health Sciences, the National Cancer Institute, and the National Center for Toxicological Research. The Committee recommends that task forces follow the same guidelines used by the regulatory agencies. Joint risk assessments should be subjected to independent scientific review.

For reasons presented in the discussion of Recommendation 1, the Committee believes that such an ad hoc approach is preferable to creation of a centralized risk assessment body.

IMPROVING RISK ASSESSMENT THROUGH UNIFORM INFERENCE GUIDELINES

RECOMMENDATION 5

Uniform inference guidelines should be developed for the use of federal regulatory agencies in the risk assessment process.

In the Committee's judgment, the development of uniform inference guidelines is feasible and desirable. However, the Committee emphasizes that guidelines cannot provide a formula for automatically calculating risk from available data; case-by-case scientific interpretation will still be crucial, and risk assessments must reflect experts' characterizations of the quality of the data and of the uncertainty associated with the final assessment.

Adherence to uniform guidelines has several advantages over ad hoc performance of risk assessments. Guidelines could help to separate risk assessment from risk management considerations, improve public understanding of the process, foster consistency, and prevent oversights and judgments that are inconsistent with current scientific thought. The development and application of guidelines would help to focus discussion by the public and the scientific community on the generic issues of risk assessment, outside the sometimes charged context of particular regulatory decisions. Such discussion could stimulate research interest and lead to evolutionary improvement in the guidelines and thus in the quality of

risk assessment--improvement that would not occur if risk assessments were performed on an ad hoc basis. Guidelines also provide an efficient means to ensure the quality and relevance of data generated in new bioassay, epidemiologic, and other pertinent studies on the toxicity of particular chemicals, thus improving the scientific data base for future risk assessments of those chemicals. Guidelines can also help regulated parties to know in advance the criteria that agencies will apply in evaluating substances. Industry would benefit if all federal agencies used the same guidelines. Furthermore, uniform federal guidelines could help to harmonize the current development of risk assessment methods by an increasing number of state programs.

Uniform guidelines should be prepared for hazard identification, dose-response assessment, and risk characterization. Government-wide guidelines for exposure assessment may be impractical, and this aspect of risk assessment is treated separately in Recommendation 9.

The Committee is aware of several arguments to the effect that uniform guidelines could have adverse effects. We believe, however, that well-designed and carefully applied guidelines will minimize these disadvantages.

RECOMMENDATION 6

The inference guidelines should be comprehensive, detailed, and flexible. They should make explicit the distinctions between the science and policy aspects of risk assessment. Specifically, they should have the following characteristics:

- **They should describe all components of hazard identification, dose-response assessment, and risk characterization and should require assessors to show that they have considered all the necessary components in each step.**
- **They should provide detailed guidance on how each component should be considered, but permit flexibility to depart from the general case if an assessor demonstrates that an exception is warranted on scientific grounds.**
- **They should provide specific guidance on components of data evaluation that require the imposition of risk assessment policy decisions and should clearly distinguish those decisions from scientific decisions.**

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 29 of 48

- They should provide specific guidance on how an assessor is to present the results of the assessment and the attendant uncertainties.

Distinguishing Science from Policy

A frequent deficiency of agency risk assessments is the failure to distinguish between scientific and policy considerations in risk assessment. Critics contend that the results of risk assessment are often seen as scientific findings by regulators and the public, whereas in fact they are based in part on other considerations. The Committee believes that guidelines can lead to risk assessments that clearly delineate the limits of current scientific knowledge and the policy basis for choosing among inference options.

Comprehensive and Detailed Nature

Comprehensive, detailed guidelines are needed to delineate risk assessment as a process distinct from risk management. Comprehensive guidelines are those which address all components of risk assessment that are subject to generic treatment. Detailed guidelines are those which provide substantial supplementary scientific discussion of each component. Such discussion helps to reduce the possibility that analysts will misuse guidelines as cookbook instructions and helps analysts to anticipate special conditions for which particular inference options are appropriate or inappropriate.

Broad statements of principle are inadequate, because they leave components undefined and may permit excessive discretion in particular cases. An explicit, comprehensive statement has the advantages of improving public understanding of government risk assessment and of assisting regulated parties to anticipate government actions.

Another reason for specifying comprehensive, detailed guidelines is that they hold the greatest promise of preventing inconsistency within and among agencies. At numerous points in a risk assessment, different risk assessors may select different (but scientifically valid) inference options; guidelines should specifically address each of these. A related advantage is an improvement in quality control that could occur if all assessors were

required to consider the broad range of issues addressed in such guidelines; that would decrease the likelihood that important considerations would be neglected or that uninformed judgment would occur.

Flexibility

The Committee espouses flexible guidelines. Rigid guidelines, which permit no variation, might preclude the consideration of relevant scientific information peculiar to a particular chemical and thus force assessors to use inference options that are not appropriate in a given case. Also, rigid guidelines might mandate the continued use of concepts that become obsolete with new scientific developments. Large segments of the scientific community would undoubtedly object to such guidelines as incompatible with the use of the best scientific judgment for policy decisions.

Flexibility can be introduced by the incorporation of default options. The assessor would be instructed to use a designated (default) option unless specific scientific evidence suggested otherwise. The guidelines would thus permit exceptions to the general case, as long as each exception could be justified scientifically. Such justifications would be reviewed by the scientific review panels and by the public under procedures described above. Guidelines could profitably highlight subjects undergoing relatively rapid scientific development (e.g., the use of metabolic data for interspecies comparisons) and any other components in which exceptions to particular default options were likely to arise. They should also attempt to present criteria for evaluating whether an exception is justified.

Presenting the Results of the Assessment

Conclusions based on a large number of sequential, discretionary choices necessarily entail a large, cumulative uncertainty. The degree of uncertainty may be masked to some extent when, in the final form of an assessment, risk is presented as a number with an associated measure of statistical significance. If they are to be most instructive to decision-makers, assessments should provide some insight into qualitative characteristics of the data and interpretations that may impute more or less certainty to the final results.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 30 of 48

RECOMMENDATION 7

The process for developing, adopting, applying, and revising the recommended inference guidelines for risk assessment should reflect their dual scientific and policy nature:

- An expert board should be established to develop recommended guidelines for consideration and adoption by regulatory agencies. The board's recommended guidelines should define the scientific capabilities and limitations in assessing health risks, delineate subjects of uncertainty, and define the consequences of alternative policies for addressing the uncertainties.
- The expert board's report and recommendations should be submitted to the agencies responsible for regulating the hazards addressed by the guidelines for their evaluation and adoption. The agencies, perhaps with central coordination, should, when possible, choose a preferred option from among the options that are consistent with current scientific understanding. The procedures for adoption should afford an opportunity for members of the public to comment.
- The process followed by the government for adoption of inference guidelines should ensure that the resulting guidelines are uniform among all responsible agencies and are consistently adhered to in assessing the risks of individual hazards.
- The resulting uniform guidelines should govern the performance of risk assessments by all the agencies that adopt them until they are re-examined and revised; they should not prevent members of the public from disputing their soundness or applicability in particular cases. In short, the guidelines should have the status of established agency procedures, rather than binding regulations.
- The guidelines should be reviewed periodically with the advice and recommendations of the expert board. The process for revising the guidelines, like the process for adoption, should afford an opportunity for comment by all interested individuals and organizations.

Inference guidelines for risk assessment are based largely on science, but other considerations are involved in components with substantial scientific uncertainty. For these, the choice among inference options can have substantial policy ramifications. Thus, we recommend a

two-step process in which a board of experts recommends guidelines and provides scientific commentary on available inference options and then the government adopts final guidelines based in part on the board's recommendations.

The Board and Its Role

The recommended guidelines should be developed by a congressionally chartered board of experts who are independent of regulatory policy-making. We describe this board, its placement, and other functions that it can serve in Recommendation 10. In general terms, the board should be permanent, should represent professional excellence on a national scale, and should have facility with issues that have policy ramifications. We see advantages in locating the board outside the government.

The board's role is mainly scientific. It should define the components of risk assessment and describe the scientific basis for each. When it finds general scientific agreement on the proper inference option for a component, it should designate that option in a recommended guideline. When the board finds no general scientific agreement on the available inference options, it should recommend against the use of options that are scientifically unsupportable and comment on the relative strength of the scientific support for the options that remain.*

Agency Adoption

The Committee envisions that the second step in the establishment of guidelines will be in the hands of the

*Some members of the Committee believe that the board should also be encouraged in such cases to recommend the option that it judges to have the most scientific support, as long as the board clearly indicates that such choices are based on members' informed scientific judgment, not on general agreement in the scientific community. Other Committee members believe that such recommendations would imply scientific certainty where none exists and thus would result in scientists' improperly recommending policy on the basis of their subjective judgments.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 31 of 48

government. The choice of guidelines is, ultimately, the responsibility of duly elected or appointed public officials, and public review and comment on the proposed guidelines should be completed before they are adopted. The Committee emphasizes that, to be most useful, the final guidelines should prescribe default options for all components of risk assessment. Thus, the second step should further limit the inference options available to the agencies, even for components in which the board found that no single option could be chosen on scientific grounds. In that case, full consideration should be given to the board's comments on the merit of the scientific support that is available for each option.

It is important that the process result in a timely, uniform set of inference guidelines to be used by all agencies. We thus see advantage in coordination of the agencies' adoption of guidelines by a single, central authority such as the Office of Science and Technology Policy, or by a mechanism designated by Congress.

The Committee believes that adopting the guidelines as established procedures, rather than as formal regulations, would have several important advantages: it would allow guidelines to be adopted and amended more easily; it would bind the agencies to adhere to the guidelines until they were reviewed and revised (thus fostering predictability and consistency--any agency's failure to comply with its own guidelines could be noted by independent scientific review panels and could be cited as grounds for interested parties' legal appeal of an associated regulatory decision); and it would permit members of the public to advocate new or alternative approaches to risk assessment.

Joint risk assessments performed by interagency task forces should be governed by the guidelines that emerge from this process.

Uniformity

The Committee has presented its case for uniformity in guidelines: consistency in the conduct of risk assessment reduces the appearance of unfair and inconsistent regulatory policies, improves priority-setting among regulators' programs, increases public understanding, and provides coherence for those subject to various regulatory authorities. A frequent argument against government-wide guidelines is that different agencies have statutory responsibilities that reflect different social policies and therefore require different approaches to risk assessment. This argument reflects a misunderstanding of the purpose of guidelines. An agency would remain free to incorporate whatever social judgments are embodied in its mandate when deciding whether and how to regulate. Such risk management choices can be made independently of and after the completion of a risk assessment. Thus, two agencies could use the same risk assessment of a substance, but regulate it differently on the basis of statutory or policy criteria applied after risk assessment.

Periodic Review

The scientific basis of risk assessment is evolving rapidly. Guidelines must continue to evolve to accommodate scientific innovations and theories. By their very nature, guidelines themselves will help to foster evolutionary improvements by defining generic principles of risk assessment and focusing debate and empirical research on these principles.

Furthermore, new public perceptions of risk occur, and guidelines will evolve in response to these changes as well. For example, attitudes about the practicality of the outright elimination of carcinogenic risk as a regulatory goal have changed in the last decade. New methods of quantitative risk assessment have developed, and public discussions have increasingly focused on that field. These changes can be expected to continue, so regular periodic review of guidelines appears to be essential. Such review should follow the same procedures recommended for the initial guidelines, including ultimate agency adoption after public comment.

RECOMMENDATION 8

The Committee recommends that guidelines initially be developed, adopted, and applied for assessment of cancer risks. Consideration of other types of health effects should follow. It may not yet be feasible to draw up as complete a set of inference guidelines for some other health effects. For these, defining the extent of scientific knowledge and uncertainties and suggesting methods for dealing with uncertainties would constitute a useful first step.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 32 of 48

The Committee believes that guidelines for carcinogenic risk assessment should be drawn up first, both because cancer is perceived as a major public-health hazard and because there is considerable experience with carcinogenic risk assessment from which to draw. Several guideline documents for carcinogenic risk assessment have already been produced, and review of these documents and of their history should provide a useful point of departure.

However, the other health effects that result from exposure to hazardous substances are equally amenable to prevention by regulatory action. Guidelines are desirable for these types of effects, which include mutagenicity, reproductive and teratogenic effects, neurotoxicity, and behavioral changes. Less information (and, in some cases, less knowledge of causal mechanisms) is usually available on these effects. In fact, in some situations where the knowledge base is less adequate than in cancer, stipulated methods for handling scientific uncertainty may be even more important. Risk assessments for cancer are likely more frequently to engage the problems of evaluating data on exposure of experimental animals, whereas many other health effects will require greater reliance on epidemiologic evidence.

The Committee believes that the absence of guidelines for a health effect is not a justification for agency failure to perform risk assessments or to regulate on a case-by-case basis.

RECOMMENDATION 9

Agencies should develop guidelines for exposure assessment. Because of diverse problems in estimating different means of exposure (e.g., through food, drinking water, and consumer products), separate guidelines may be needed for each.

Operating assumptions are needed to estimate exposures when direct measurements cannot be obtained. Examples of cases in which such estimates would be important are the projection of exposure to new chemicals and determination of the exposure reduction that would result from implementation of a particular control option. In only a few narrow cases (e.g., food additives) have general guidelines been developed for exposure assessment.

Although they are no less important than techniques for hazard identification and dose-response assessment,

exposure assessment techniques have not been the subject of major scientific debate and scrutiny. For example, if exposure were known more accurately, priority-setting for testing new chemicals or for initiating regulation of one of a group of chemicals could be organized on a more rigorous basis; consideration of both the apparent potency and the estimated exposure would be factored into such decisions.

Exposure assessment guidelines that are uniform across federal programs may not be feasible, because of the diversity of media that must be addressed and the large variation in exposures. Medium-specific exposure models (such as dispersion models for air, water, and soil) are used by programs in the agencies with various degrees of sophistication and validation. Each agency or each program in an agency should develop medium-specific guidelines to stimulate evolutionary improvement, increase consistency and predictability, and isolate the choice among inference options from inappropriate risk management considerations. Two or more programs that deal with a given medium of exposure should use the same guidelines.

Agencies should make their proposed exposure assessment guidelines available for public comment and should subsequently issue final guidelines as established procedures.

A CENTRAL BOARD ON RISK ASSESSMENT METHODS

RECOMMENDATION 10

The Committee recommends to Congress that a Board on Risk Assessment Methods be established to perform the following functions:

- To assess critically the evolving scientific basis of risk assessment and to make explicit the underlying assumptions and policy ramifications of the different inference options in each component of the risk assessment process.
- To draft and periodically to revise recommended inference guidelines for risk assessment for adoption and use by federal regulatory agencies.
- To study agency experience with risk assessment and evaluate the usefulness of the guidelines.
- To identify research needs in the risk assessment field and in relevant underlying disciplines.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 33 of 48

To avoid possible misunderstanding of the role of the Board, the Committee stresses the limitations on proposed Board activities. The Board would not perform or review individual risk assessments, nor would it adjudicate disputes arising from regulatory actions related to specific substances. Thus, the Board as envisioned would not perform functions contemplated by the AIHC proposal or H.R. 638. A central board of distinguished expert advisors is not well-suited to such day-to-day responsibilities. Furthermore, we believe strongly that it would be inappropriate to remove such essential analytic functions from the responsible agencies and that it would be wasteful to duplicate agency activities.

The Board would make its contributions through discussion of contending scientific positions, preparation of recommended uniform guidelines, and fostering of advancement of the field. It would fill a need for a prestigious, independent locus of activity for improving the understanding of generic issues in both the scientific basis and the federal practice of risk assessment. Current ad hoc approaches too often color debate on general issues with the implications for particular, often contentious, risk management decisions. We expect that Board activities would improve the scientific performance of the agency processes and, in conjunction with other mechanisms we recommend, achieve greater objectivity and consistency and better public understanding of risk assessment. The Board would be the body to which agencies, agency review panels, and others would turn both for periodic recommendations of guideline revisions and for information on the evolving art of risk assessment.

Board Functions

We foresee four major functions for the Board. The first two, scientific review and development of recommended guidelines, would pursue the process described above for the initial generation of inference guidelines (Recommendation 7). The drafting of guidelines by the Board would ensure that guidelines benefit from the best available scientific knowledge and judgment. After recommended guidelines for a particular health effect were prepared and referred to the agencies for review and adoption, the Board would probably find it useful to continue its activity in the review of scientific developments relevant to risk assessment for that effect.

The Board's third function would involve observation of and research into federal experience with risk assessment generally and review of the usefulness of guidelines. A major purpose would be to acquaint the Board with ways of improving the guidelines in later periodic reviews.

As a fourth function, the Board would identify the key scientific research needs in health risk assessment. Preparation of guidelines would put the Board in an ideal position to understand which of the many inference options needed to cover gaps in scientific understanding are most important and are amenable to study. The policy difficulties in regulating chronic health hazards can be resolved only if uncertainty in the scientific basis of assessments is reduced. Board activities could take such forms as advising funding agencies on research priorities, commissioning survey papers to synthesize recent scientific findings, and sponsoring conferences or special publications on particularly apt scientific questions or on matters that are important to risk assessment, but have been neglected by the scientific community. In addition, the Board's experience would place it in an ideal position to assess whether and how toxicologic research on particular chemicals could be better tailored to the analytic needs of future risk assessors. For example, many current testing procedures were designed for the narrow purpose of hazard identification, and adjustments in these procedures could lead to more definitive dose-response assessments.

The Committee believes that the responsibilities of the Board could be discharged by a group of volunteer experts that convened monthly for 1-2 days.

Organizational Placement

The proper placement of the Board would be crucial to its prospects for success. There are four criteria for identifying appropriate locations: professional excellence, facility with studies having substantial policy ramifications, permanence, and independence.

Professional excellence is important because the Board's recommended guidelines, as well as its other work, should be based on the best available science; the Board should be able to attract the best talent in the nation. Facility with difficult policy issues is important because risk assessment is not a strictly scientific undertaking, and it would be crucial for the Board to

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 34 of 48

conduct its work competently and with full understanding of the policy process. Placement in a permanent, existing organization is advisable because the Board should be able to begin its work quickly and remain stable in order to conduct periodic revisions of guidelines. Independence is needed to provide credibility; work that is suspected of bias will not transcend the current atmosphere of distrust. We see advantages in placing the Board outside the government. In particular, the Board should be able to draw on the widest pool of scientific experts and not be restricted to government scientists; placement in the government might hinder the perception that the Board is free from the policy orientation of the administration in power; and direct involvement by the regulatory agencies themselves could detract from their ability to make regulatory decisions while the guidelines were in preparation.

The Committee has evaluated a number of possible organizational bases for the Board. The National Toxicology Program has had relevant experience with the scientific basis of risk assessment, but it already has major responsibility for coordinating testing of chemicals of interest to regulatory agencies. The Congressional Office of Technology Assessment is another possibility. However, the governance of the Office of Technology Assessment by a board composed of members of Congress could prove a practical impediment to the production of guidelines. Guidelines would clearly have policy ramifications that may be at variance with the established policy positions of OTA board members. The Office of Science and Technology Policy or the Office of Management and Budget could provide government-wide coordination; both are in the Executive Office of the President and are well positioned to ensure agency response and uniform implementation of guidelines and other Board findings. The major disadvantage of location in the Executive Office of the President is the lack of independence and, consequently, the greater likelihood of mixing scientific and policy considerations. All these organizations share the major drawback that they are in the government.

A special-purpose national (or Presidential) commission on risk assessment methods could attract eminent scientists to service and could be designed to balance viewpoints, but would lack permanence and policy experience. Professional societies constitute another class of possible candidates, but they generally have limited familiarity with policy studies.

We conclude that the National Academy of Sciences-National Research Council meets the four criteria for placement. The AIHC proposal addressed the same general concerns that have occupied this Committee and concluded that the most appropriate locus for the central panel was in the NAS-NRC. Although we do not concur in the idea of centralizing the performance of risk assessments, the arguments presented by the AIHC proposal for the selection of the NAS-NRC are fully applicable to the question of the placement of a Board that would address generic scientific issues in risk assessment. We believe that the Board could best function under NAS-NRC auspices, if the NAS-NRC agreed to provide them, and would be of great value in achieving many of the goals that we share with the authors of the AIHC proposal and of H.R. 638. Current NAS-NRC procedures for establishing, managing, and issuing study reports are appropriate for the prospective Board.

Qualifications of Members

We recommend that the Board consist of scientists with training and experience in the various disciplines involved in the process of risk assessment, including biostatistics, toxicology, epidemiology, environmental engineering, and clinical medicine. Other relevant fields--such as law, ethics, and the social sciences--should be included to ensure due appreciation of the policy context of Board activities. For the same reason, some members should have familiarity with regulatory programs. The nomination and selection of members should be in accordance with established NAS-NRC procedures. Service might be for staggered 3-year periods.

Sunset Review

The entire concept of the Board and its functions should be reviewed after approximately 6-8 years.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 35 of 48

APPENDIX A
Background Information on Committee Members

REUEL A. STALLONES, Chairman, is Dean of the University of Texas School of Public Health in Houston. Dr. Stallones is an epidemiologist specializing in studies of risk factors in cardiovascular disease and is a member of the Institute of Medicine. He is a past member of the NRC Board on Toxicology and Environmental Health Hazards and has served on several NRC committees that evaluated the risks of environmental pollutants.

MORTON CORN is Director of the Division of Environmental Health Engineering at the School of Hygiene and Public Health, The Johns Hopkins University. He specializes in evaluation and engineering control of airborne chemical agents in the workplace and the atmosphere. Dr. Corn served as the Assistant Secretary of Labor for Occupational Safety and Health from October 1975 to January 1977. He is a member of the Panel of Experts in Occupational Health of the World Health Organization and serves on committees of EPA's Science Advisory Board and the Congressional Office of Technology Assessment.

KENNY S. CRUMP is President of Science Research Systems, Inc., a consulting firm specializing in the evaluation of statistical data and risk assessment. His work on methods of extrapolating from high to low doses is used by EPA's Carcinogen Assessment Group. He was previously with Louisiana Tech University where he was Professor of Mathematics and Statistics.

J. CLARENCE DAVIES is Executive Vice President of the Conservation Foundation. He has served on other NRC

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 36 of 48

committees dealing with regulatory issues, was chairman of the NRC Committee on Principles of Decision Making for Regulating Chemicals in the Environment (1974-1975), and now serves on the Environmental Studies Board. Dr. Davies served for 6 years as a member of the Executive Committee of EPA's Science Advisory Board.

VINCENT P. DOLE is Professor of Medicine at Rockefeller University and conducts research on addictive behavior and metabolic diseases. Dr. Dole is a member of the National Academy of Sciences and has served as an NAS reviewer of a number of risk-related studies.

TED R. I. GREENWOOD is Associate Professor of Political Science at MIT. He has served as a Senior Policy Analyst in the Office of Science and Technology Policy (1977-1979). Dr. Greenwood has written about the problem of nuclear waste disposal and recently completed a monograph on the interaction between knowledge and discretion in regulatory decision-making.

RICHARD A. MERRILL is Dean of the Law School of the University of Virginia. He has been on the Law School faculty since 1969, except for 2 years (1975-1977), when he served as Chief Counsel to the FDA. He recently completed a study of regulatory decision-making on carcinogens for the Administrative Conference of the United States that focused on FDA's regulation of food contaminants, CPSC's regulation of chronic hazards, OSHA's program for workplace carcinogens, and the EPA pesticides program. Dean Merrill is a member of the Institute of Medicine and the NRC Board on Toxicology and Environmental Health Hazards. He teaches food and drug law, environmental health regulation, and administrative law.

FRANKLIN E. MIRER is Director of the Health and Safety Department of the International Union, United Auto Workers. Dr. Mirer, an industrial hygienist and toxicologist, has been with the UAW since 1975. He specializes in issues related to workplace chemical exposures and development of OSHA standards.

D. WARNER NORTH is a Principal with Decision Focus, Inc., a consulting firm specializing in decision analysis, and consulting Associate Professor with the Department

of Engineering-Economic Systems at Stanford University. Over the last 15 years, Dr. North has carried out applications of decision analysis and risk assessment to a variety of public-policy issues. He has participated in three previous NRC studies on air quality and toxic chemicals. His recent projects include work on methods for setting priorities and developing a regulatory strategy for toxic chemicals for the EPA Office of Toxic Substances. Dr. North has served on committees of the EPA Science Advisory Board since 1977.

ILBERT S. OMENN is Dean of the School of Public Health of the University of Washington in Seattle. A physician and geneticist, Dr. Omenn served in senior positions in the Office of Science and Technology Policy and in the Office of Management and Budget (1977-1981). He is a member of the Institute of Medicine. At OSTP, he was concerned with federal decision-making for public-health risks and was coauthor of a paper on the process for making such decisions. Before returning to the University of Washington, Dr. Omenn was a Fellow at the Brookings Institution, where he analyzed EPA's 1979 decision to revise the national ambient air quality standard for photochemical oxidants (measured as ozone).

)SEPH V. RODRICKS is a Principal with ENVIRON Corporation, a Washington, D.C., consulting firm specializing in risks related to exposure to toxic substances. Dr. Rodricks, a biochemist, was with the FDA for 15 years (1965-1980). While at FDA, he served as Deputy Associate Commissioner and as chairman of an interagency work group on risk assessment that developed guidelines for member agencies to follow for determining risks associated with exposure to carcinogenic chemicals. Dr. Rodricks is a member of the NRC Board on Toxicology and Environmental Health Hazards and a Diplomate of the American Board of Toxicology.

AUL SLOVIC is a psychologist at Decision Research in Eugene, Oregon. His research interests are related to human judgment in decision-making, with special emphasis on perception of risk, and he is coauthor of a book on the concept of acceptable risk. Dr. Slovic has served as a consultant to FDA, NSF, the National Institute of Mental Health, and the Nuclear Regulatory

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 37 of 48

Commission. He has been a council member of the Society for Risk Analysis and is President-elect of that organization.

H. MICHAEL D. UTIDJIAN is Corporate Medical Director at the American Cyanamid Company. Dr. Utidjian has been active in occupational medicine since 1961. Before gaining his current position, he was a Staff Scientist at Stanford Research Institute and served as a consultant to NIOSH. He also served as Associate Corporate Medical Director at Union Carbide.

ELIZABETH WEISBURGER is Assistant Director for Chemical Carcinogenesis at the National Cancer Institute. Dr. Weisburger, a toxicologist/oncologist, has been at NCI for 33 years and was involved in initial NCI decisions on establishing its bioassay program and determining which compounds to test.

APPENDIX B
Bibliography

A. GUIDELINES AND POLICY FOR RISK ASSESSMENT

Albert, R. E., R. Train, and E. Anderson. Rationale Developed by EPA for the Assessment of Carcinogenic Risks. Journal of the NCI Vol. 58, No. 5, May 1977, pp. 1537-1541.

Calkins, D. R., R. L. Dixon, C. R. Gerber, D. Zarin, and G. S. Omenn. Identification, Characterization and Control of Potential Human Carcinogens: A Framework for Federal Decision-Making. Journal of the NCI Vol. 64, No. 1, January 1980, pp. 169-176.

Consumer Product Safety Commission. Interim Policy and Procedure for Classifying, Evaluating, and Regulating Carcinogens in Consumer Products. Federal Register Vol. 43, No. 114, June 13, 1978, pp. 25658-25665.

Department of Labor, Occupational Safety and Health Administration. Identification, Classification, and Regulation of Potential Occupational Carcinogens. Federal Register Book 2 of 2, Vol. 45, No. 15, January 22, 1980, pp. 5001-5296.

Environmental Protection Agency. Health Risk and Economic Impact Assessments of Suspected Carcinogens: Interim Procedures and Guidelines. Federal Register Vol. 41, No. 102, May 25, 1976, pp. 21402-21405.

Environmental Protection Agency. Mutagenicity Risk Assessments; Proposed Guidelines. Federal Register Vol. 45, No. 221, November 13, 1980, pp. 74984-74988.

Food and Drug Administration. Chemical Compounds in Food Producing Animals: Criteria and Procedures for Evaluating Assays for Carcinogenic Residues. Federal Register Vol. 44, No. 55, May 20, 1979, pp. 17070-17114.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 38 of 48

International Agency for Research on Cancer. General Principles for Evaluating the Carcinogenic Risk of Chemicals. In Evaluation of the Carcinogenic Risk of Chemicals to Humans. IARC, Lyon, France, Vols. 1-29, 1972-1982.

Interagency Regulatory Liaison Group. Work Group on Risk Assessment. Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks. Journal of the NCI Vol. 63, No. 1, July 1979, 25 pp. and Abstract.

March of Dimes Birth Defects Foundation. Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards; Proceedings of Conference. Washington, D.C., January 26-27, 1981, 163 pp.

National Academy of Sciences. Committee for a Study on Saccharin and Food Safety Policy. Food Safety Policy: Scientific and Social Considerations. NAS-NRC, March 1979.

National Academy of Sciences. Committee on the Biological Effects of Ionizing Radiations. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. NAS-NRC, 1980, 638 pp.

National Cancer Advisory Board. General Criteria for Assessing the Evidence of Carcinogenecity of Chemical Substances. Report of the Subcommittee on Environmental Carcinogenesis, NCAB. Journal of the NCI Vol. 58, No. 2, February 1977, pp. 461-465.

State of California, Health and Welfare Agency. Carcinogen Identification Policy: A Statement of Science as a Basis of Policy; Section 2: Methods for Estimating Cancer Risks from Exposure to Carcinogens. October 1982.

U.S. Regulatory Council. Statement on Regulation of Chemical Carcinogens: Policy and Request for Public Comments. Federal Register Part IV, Vol. 44, No. 202, October 17, 1979, pp. 60038-60049.

B. SUGGESTIONS FOR PROCEDURAL REFORM

Albert, R. A. Toward a More Uniform Federal Strategy for the Assessment and Regulation of Carcinogens. Report to the Office of Technology Assessment, 1980.

American Industrial Health Council. AIHC Proposal for a Science Panel (mimeo), March 12, 1981, 9 pp. and Appendix, AIHC Recommended Framework for Identifying Carcinogens and Regulating Them in Manufacturing Situations, October 11, 1979, 11 pp.

American Industrial Health Council. Comparative Analysis of H.R. 6521 (Wampler Bill) and Science Panel Proposal, March 3, 1980.

American Industrial Health Council. Critical Evaluation of Proposals by the AIHC to Strengthen the Scientific Base for Regulatory Decisions; Report of the Scientific Workshop (mimeo), August 1982, 6 pp.

American Industrial Health Council. Proposals for Improving the Science Base for Chronic Health Hazard Decision-Making, December 2, 1981, 29 pp. and Appendixes.

Banks, R. The Science Court Proposal in Retrospect: A Literature Review and Case Study. Critical Reviews in Environmental Control Vol. 10, August 1980, pp. 95-131.

Barr, J. T., D. H. Hughes, and R. C. Barnard. The Use of Risk Assessment in Regulatory Decision Making: Time for a Review. Regulatory Toxicology and Pharmacology Vol. 1, 1981, pp. 264-276.

Bazelon, D. L. Risk and Responsibility. Science Vol. 205, July 20, 1979, pp. 277-280.

Boffey, P. M. Science Court: High Officials Back Test of Controversial Concept. Science Vol. 194, October 8, 1976, pp. 167-169.

Deisler, P. F., Jr. Dealing with Industrial Health Risks: A Step-Wise, Goal-Oriented Concept. In Risk in the Technological Society, Hohenemser and Kasperson, eds. Westview Press, 1981.

Food Safety Council. Social and Economic Committee. A New Approach: Principles and Processes for Making Food Safety Decisions. FSC, 1981, 103 pp. plus Appendixes.

Food Safety Council. A Proposed Food Safety Evaluation Process: Final Report of Board of Trustees. FSC, June 1982, 142 pp.

General Accounting Office. Improving the Scientific and Technical Information Available to the EPA in Its Decision-making Process. Report CED-79-115, September 1979, 60 pp.

Gori, G. B. Regulation of Cancer-Causing Substances: Utopia or Reality. Chemical and Engineering News September 6, 1982, pp. 25-32.

Gori, G. B. The Regulation of Carcinogenic Hazards. Science Vol. 208, April 18, 1980, pp. 256-261.

H.R. 638 (Wampler Bill). National Science Council Act of 1981. Introduced January 8, 1981.

H.R. 6159 (Ritter Bill). Risk Analysis Research and Demonstration Act of 1982. Introduced April 26, 1982.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 39 of 48

Kantrowitz, A. Controlling Technology Democratically. American Scientist Vol. 63, 1975, pp. 505-509.

Kantrowitz, A. Proposal for an Institution for Scientific Judgment. Science Vol. 156, May 12, 1967, pp. 763-764.

Markey, H. T. Testimony to the Subcommittee on Science Research and Technology, 1979. In Risk/Benefit Analysis in the Legislative Process. U.S. Government Printing Office, Washington, D.C., 1979.

Martin, J. Procedures for Decision Making Under Conditions of Scientific Uncertainty: The Science Court Proposal. Harvard Journal of Legislation Vol. 16, Spring 1979, pp. 443-511.

National Academy of Sciences. Committee on Environmental Decision Making. Decision Making in the Environmental Protection Agency. NAS-NRC, 1977, 250 pp.

National Academy of Sciences. Committee on Food Protection, Food and Nutrition Board. Risk Assessment/Safety Evaluation of Food Chemicals. NAS-NRC, 1980, 36 pp.

National Academy of Sciences. Committee on Prototype Explicit Analyses for Pesticides. Regulating Pesticides. NAS-NRC, 1980, 237 pp.

National Academy of Sciences. Committee on Toxicology. Principles and Procedures for Evaluating the Toxicity of Household Substances. NAS-NRC, 1977, 130 pp.

National Academy of Sciences. Environmental Studies Board/Committee on Toxicology. Principles for Evaluating Chemicals in the Environment. NAS-NRC, 1975.

Ramo, S. Regulation of Technical Activities: A New Approach. Science Vol. 213, Aug. 21, 1981, pp. 837-842.

Rowe, W. D. Regulation of Toxic Chemicals Within the Limits of Knowledge. Report submitted to the Office of Technology Assessment, 1980.

S. 1442 (Hatch Bill). Food Safety Amendments of 1981. Introduced June 25, 1981.

Squire, R. A. Ranking Animal Carcinogens: A Proposed Regulatory Approach. Science Vol. 214, 1981, pp. 877-880.

Toxic Substances Strategy of Committee. Report to the President: Toxic Chemicals and Public Protection. U.S. Government Printing Office, Washington, D.C., 1980.

U.S. House of Representatives. Omnibus Budget Reconciliation Act of 1981: Conference Report. Report 97-208, July 1981, pp. 383-384, 881-883.

U.S. House of Representatives. Committee on Agriculture. The National Science Council Act, June 1981.

U.S. House of Representatives. Committee on Science and Technology. Risk Analysis Research and Demonstration Act of 1982. Report No. 97-625, June 24, 1982.

Wessel, M. R. Science and Conscience. Columbia University Press, 1980, 140 pp.

C. SCIENTIFIC AND POLICY BASIS OF RISK ASSESSMENT

Ames, B. N. Identifying Environmental Chemicals Causing Mutations and Cancer. Science Vol. 204, May 22, 1979, pp. 587-593.

Anderson, E. L. Quantitative Methods in Use in the United States to Assess Cancer Risk. Paper presented at the Workshop on Quantitative Estimation of Risk to Human Health from Chemicals, Rome, Italy, July 12, 1982.

Anderson, E. L. Uses of Quantitative Risk Assessment by EPA (mimeo). Prepublication draft, 18 pp.

Ashford, N. A., E. M. Zolt, D. Hattis, J. I. Natz, G. R. Heaton, and W. C. Priest. Evaluating Chemical Regulations: Trade-off Analysis and Impact Assessment for Environmental Decision-Making (mimeo). MIT Center for Policy Alternatives, 1979.

Baram, M. S. Cost-Benefit Analysis: An Inadequate Basis for Health, Safety, and Environmental Regulatory Decisionmaking. Ecology Law Quarterly Vol. 8, No. 3, 1980, pp. 473-531.

Campbell, G., D. Cohan, and D. W. North. The Application of Decision Analysis to Toxic Substances: Proposed Methodology and Two Case Studies. Prepared for EPA by Decision Focus Incorporated, 1981.

Cornfield, J. Carcinogenic Risk Assessment. Science Vol. 198, November 18, 1977, pp. 693-699.

Crandall, R. W., and L. B. Lave, eds. The Scientific Basis of Health and Safety Regulation. Brookings Institution, 1981, 309 pp.

Crouch, E., and R. Wilson. Interspecies Comparison of Carcinogenic Potency. Journal of Toxicology and Environmental Health Vol. 5, 1979, pp. 1095-1118, plus Appendixes.

Crouch, E., and R. Wilson. Regulation of Carcinogens. Risk Analysis Vol. 1, 1981, pp. 47-57; discussion pp. 59-66.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 40 of 48

National Academy of Sciences. Committee on Risk and Decison-Making. Risk and Decision Making: Perspectives and Research. NAS-NRC, 1982 68 pp.

National Academy of Sciences. Governing Board; Committee on the Assessment of Risks. The Handling of Risk Assessments in NRC Reports (mimeo.). March 1981, 27 pp.

Nicholson, W. J., ed. Management of Assessed Risk for Carcinogens. New York Academy of Sciences, 1981, 301 pp.

Nisbet, I. C. T., and N. J. Karch. Chemical Hazards to Human Reproduction. Noyes Data, Park Ridge, N.J., 1983.

Office of Technology Assessment. Assessment of Technologies for Determining Cancer Risks from the Environment. Office of Technology Assessment, June 1981, 240 pp.

Oak Ridge National Laboratory/Environmental Protection Agency. Assessment of Risks to Human Reproduction and to Development of Human Conceptus from Exposure to Environmental Substances. ORNL/EIS-197, EPA/9-82-001, February 1982, 158 pp.

Omenn, G. S. Risk Assessment and Environmental Policy-Making: An Overview. Presentation at the seminar sponsored by George Washington University Graduate Program in Science, Technology, and Public Policy and by the EPA, Washington, D.C., January 27, 1982.

Rall, D. P. The Role of Laboratory Animal Studies in Estimating Carcinogenic Risks for Man. Address to IARC Symposium, "Carcinogenic Risks-Strategies for Intervention," Lyon, France, 1977, 12 pp.

Ricci, P. F., and L. S. Molton. Risk and Benefit in Environmental Law. Science Vol. 214, December 4, 1981, pp. 1096-1100.

Rodricks, J. V., and R. G. Tardiff. Biological Bases for Risk Assessment. Paper presented at the International Conference on Safety Evaluation and Regulation of Chemicals, Session 2: State of the Art of Safety Evaluation, Boston, Mass., February 24-26, 1982.

Rowe, W. D. An Anatomy of Risk. Wiley-Interscience, New York, 1977.

Samuels, S. W. Determination of Cancer Risk in a Democracy. Annals of the New York Academy of Sciences Vol. 271, 1976, pp. 421-430.

Thomas, L., S. J. Farber, R. A. Doherty, A. Koppas, and A. A. Upton. Report of the Governor's Panel to Review Scientific Studies and the Development of Public

Policy on Problems Resulting from Hazardous Wastes (mimeo). New York State, October 1980, 33 pp.

Van Ryzin, J. Quantitative Risk Assessment. Journal of Occupational Medicine Vol. 22, No. 5, May 1980, pp. 321-326.

Weinberg, A. M. Science and Trans-Science. Minerva No. 10, 1972, pp. 202-222.

Weisburger, J. H., and G. M. Williams. Carcinogen Testing: Current Problems and New Approaches. Science Vol. 214, October 23, 1980 pp. 401-407.

D. BIBLIOGRAPHIES

Krewski, D., and C. Brown. Carcinogenic Risk Assessment: A Guide to the Literature. Biometrics Vol. 37, June 1981, pp. 353-366.

Tardiff, R. G. Extrapolation: High to Low Doses (mimeo). National Academy of Sciences, September 1981, 5 pp.

Tardiff, R. G. Extrapolation: High to Low Doses Combined with Laboratory Animals to Humans (mimeo). National Academy of Sciences, October 1981, 6 pp.

Tardiff, R. G. Extrapolation. Laboratory Animals to Humans (mimeo). National Academy of Sciences, October 1981, 6 pp.

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 42 of 48

APPENDIX C
Working Papers

(Photocopies of the collected working papers of the Committee on the Institutional Means for Assessment of Risks to Public Health are available from the National Academy Press, 2101 Constitution Avenue, NW, Washington, DC 20418)

CASE STUDY: CPSC'S RISK ASSESSMENT FOR FORMALDEHYDE
William M. Stigliani

CASE STUDY: NITRITE
Catherine L. St. Hilaire

CASE STUDY: ASBESTOS RISK ASSESSMENTS BY OSHA/NIOSH AND EPA
William M. Stigliani

AN ANATOMY OF RISK ASSESSMENT
Lawrence E. McCray

CURRENT FEDERAL PRACTICE IN RISK ASSESSMENT
Lawrence E. McCray and Robert I. Field

Case 01-01139-AMC Doc 17785-3 Filed 01/08/08 Page 43 of 48

EXHIBIT 120

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re: Federal Mogul Global, Inc., *et al.*, (Bankruptcy Case No. 01-10578 (RTL))

Debtors.

THE OFFICIAL COMMITTEE OF ASBESTOS CLAIMANTS and ERIC D. GREEN, as the LEGAL REPRESENTATIVE FOR FUTURE ASBESTOS CLAIMANTS,	)	
Plaintiffs,	)	
v.	)	Civil Action No. 05-59 JHR
ASBESTOS PROPERTY DAMAGE COMMITTEE,	)	
Defendant.	)	

EXPERT REPORT OF DR. MARK A. PETERSON

PLEASE TAKE NOTICE that the attached expert report of Dr. Mark A. Peterson, dated November 29, 2004, is filed on behalf of Plaintiffs the Official Committee of Asbestos Claimants (the "ACC") and the legal representative for future asbestos personal injury and wrongful death claimants (the "Futures Representative"), in anticipation of the Asbestos Claims Estimation Hearing (the "Hearing") scheduled to commence June 14, 2005. *See* Case Management Order [D.I. 17.].

Dated: Wilmington, Delaware
April 26, 2005

CAPLIN & DRYSDALE, CHARTERED
Elihu Inselbuch
399 Park Avenue
New York, New York 10022
Telephone: (212) 319-7125
Facsimile: (212) 644-6755

-and-

CAPLIN & DRYSDALE, CHARTERED
Walter B. Slocombe
Nathan D. Finch
One Thomas Circle, N.W.
Washington, DC 20005
Telephone: (202) 862-5000
Facsimile: (202) 429-3301

-and-

CAMPBELL & LEVINE, LLC

Marla R. Eskin (No. 2989)
Kathleen J. Campbell (No. 4229)
800 N. King Street, Suite 300
Wilmington, Delaware 19801
Telephone: (302) 426-1900
Facsimile: (302) 426-9947

Attorneys for Official Committee of Asbestos Claimants

YOUNG CONAWAY
STARGATT & TAYLOR LLP

James L. Patton, Jr. (No. 2202)
Edwin J. Harron (No. 3396)
Rolin Bissell (No. 4478)
Maribeth L. Minella (No. 4185)
1000 West Street, 17th Floor
P.O. Box 391
Wilmington, Delaware 19899-0391
Telephone: (302) 571-6600
Facsimile: (302) 571-1253

Attorneys for Legal Representative for Future Asbestos Claimants

Turner and Newall Inc. Projected Liabilities for Asbestos Personal Injury Claims

Mark A. Peterson

Legal Analysis Systems

November 29, 2004

through September 2001 to forecast future claims that would be filed against T&N after October 1, 2001. This "base period" represents T&N's most current claims experience, the nearly two years immediately preceding the date of forecast, and a period that is beyond the temporal effects of the Georgine class action litigation. As Table 19 shows, propensities to sue for each type of cancer during the twenty one months of the base period were considerably higher than during the years in which the Georgine class action was sub judici and higher even then filings in 1997 and 1998 when claims deferred because of Georgine were then filed.

Forecasts of future T&N claims must take two matters into account: (1) the most recent level of claiming shown by the propensities to sue during years preceding T&N's bankruptcy filing and (2) the fact that cancer filings and propensities to sue had increased sharply as of October 1, 2001. Together these matters not only establish a starting point for forecasting future T&N cancer claims based on the most recent propensity to sue, but also suggest that propensities to sue T&N may continue to increase and exceed the levels of the base period.

Table 19: Propensities to Sue T&N, by Disease: 1992-2001 (U.S.)

Filing Year	Type of Cancer		
	Meso	Lung	Othc
1992	17.4	16.6	26.4
1993	14.0	13.8	17.9
1994	18.6	14.5	15.4
1995	12.3	15.0	28.5
1996	13.1	14.3	22.6
1997	25.9	21.5	27.7
1998	29.9	25.0	42.5
1999	30.4	23.8	32.5
2000	45.0	39.4	44.1
2001	41.2	32.5	49.3

Notes: 2001 entries based on three-fourths of that year.

The number of claims forecast for each type of cancer in each future year is derived by multiplying the number of deaths projected by Nicholson for that year by the likely propensity to sue for that cancer. The calculations that are used first to derive propensities to sue and second to forecast future claims based on these propensities to sue are stated below:

Calculation of Propensity to Sue:

$$\frac{\text{Number of Claims}}{\text{Incidence}} = \text{Propensity to Sue}$$

Forecasting Future Claims from Propensity to Sue:

$$\text{Propensity to Sue} * \text{Incidence in Future Year} = \text{Projected Claims in Future Year}$$

We forecast the number of T&N cancer filings for the first future year, the year following its